HEART FAILURE

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PREFACE TO THE SECOND EDITION

The nature and treatment of circulatory failure have continued to be the object of intensive clinical and experimental investigation. Notable advances have resulted. Exhaustion of the first edition of this book over a year ago has afforded the opportunity to incorporate this progress. The revision has involved changes in all the chapters; the type has been completely reset. Despite every effort to attain the utmost brevity consistent with clarity, the amount of new material has made considerable enlargement unavoidable

An outstanding achievement of recent clinical work has been the introduction of quantitative methods for the measurement of some of the fundamental circulatory variables in health and disease. Determination of the cardiac output, the velocity of blood flow, the venous pressure, the respiratory volumes, the circulating blood volume, and the gas contents and reaction of the arterial blood have all contributed to the elucidation of the manifestations of heart failure Especially fruitful has been the application of the principles expressed in Starling's Law of the Heart to the problems of the dilatation and compensation of the failing heart. New paths have been opened by the demonstration, that many common forms of decreased cardiac output are due to diminution in the volume of blood in active circulation rather than to impairment of the motor organs of circulation The outcome of these and other lines of investigation has been an enhancement in understanding of the dynamics of the diseased circulation that bids fair to rival the unraveling of the cardiac arrhythmias which followed in the wake of the polygraph and electrocardiograph.

Nor have these advances been purely academic, they have had their repercussions at the bedside. They enable the physician to introduce a larger element of "quantitative" thinking in the interpretation of the clinical picture and the treatment of the patient. The aim of this book is to portray these advances for the practising physician in a fashion that will aid him in his daily work, for hardly

a day passes in active general practice without encountering the problems evoked by circulatory failure on which recent studies have thrown so much light. Stress has been laid on the subdivision of the broad concept of circulatory failure, and on the analysis of the clinical pictures with regard to the rôle of the individual disturbances in the dynamics of the circulation. The separation of the cardiac and peripheral elements in circulatory failure is prerequisite to optimal treatment and has therefore been discussed in considerable detail. Especial attention has been devoted to the pathogenetic analysis of the purely clinical concept of shock, and to the description of what is here called cardiac shock.

Sight has not been lost of the limited facilities with which the general practitioner, for whom this book is primarily intended, must usually carry on. But every effort has also been made to supply the foundation of principles which, though largely based on investigations in the laboratory and clinic, forms the starting point of intelligent practice

It is a pleasure to thank my teachers and associates, to whom I am indebted on many scores Like all who have worked in Mount Sinai Hospital, I owe much to the broad erudition and clinical acumen of Dr Emanuel Libman, who has inspired and guided so much of the work of the Medical Service for over three decades. I am grateful to Drs. George Baehr, Arthur M. Master, and B. S. Oppenheimer for many kindnesses. To my friend, the late Dr. Louis Gross, I owe a debt of gratitude for instruction in cardiac pathology, a field in which he was a master. Drs. W. M. Hitzig and F. H. King have collaborated with me in several studies Drs. S. Dack and M. L. Sussman have been kind enough to help in the selection of material for illustrations. My wife has worked with me throughout the preparation of the book and has been indispensable in the final revision of the manuscript. A. M. F.

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CHAPTER I

INTRODUCTORY THE CONCEPT OF CIRCULATORY FAILURE AND THE CARDINAL CIRCULATORY SYNDROMES

THE CONCEPT OF CIRCULATORY FAILURE

In health, the volume of blood that completes the vascular circuit each minute varies within wide limits, largely dictated by the metabolic rate Thus, during severe muscular exercise the cardiac output of a trained athlete increases to as much as 900 per cent of the resting value. The maximum circulatory accomplishment of an individual leading a sedentary life is, of course, not nearly so great Nevertheless, if within the ill-defined limits of the physiological, it includes a considerable factor of safety over the circulatory requirements of the usual tenor of his life.

The term circulatory failure is used to designate curtailment of this remarkably broad power of accommodation of the circulation to the ever-varying needs of the organism To the practising physician, *circulatory failure means limitation of the activities of the patient which symptoms or signs reveal to be engendered by defective circulation of the blood.* Such a purely "symptomatic" definition must suffice, *faute de mieux,* for at least the present For interesting as have been the results of studies of exercise tolerance, vital capacity, cardiac output, cardiac work, venous pressure, circulation time, and other circulatory measurements, it will be seen in succeeding chapters that they have not furnished a numerical index of the efficiency of the circulation as sensitive as are the subjective perceptions of the patient One reason for this state of affairs is that the concept of circulatory failure is relative, the circulatory apparatus of the sedentary individual of asthenic habitus cannot be expected to rise to the heights of accomplishment reached by the trained athlete. Quite obviously, the presence of the lesser degrees of circulatory failure can be determined only in the light of "past performances," *e. g.,* whether the individual becomes breathless after climbing a number of steps which previously elicited no discomfort. When circulatory failure is of but slight degree, it may be manifested only

when the metabolic rate, and consequently the entailed work of the circulation, is increased by vigorous exercise

Nowadays, there is no need to emphasize that circulatory failure is not synonymous with disease of the circulatory apparatus. The latter may be, and often is, present for years without demonstrable circulatory failure. Valvular murmurs, high blood pressure, dilatation of the aorta, hardened radial arteries, etc., reveal disease of the organs of circulation, but do not necessarily imply circulatory failure. The latter is not present as long as there is no diminution in the amount of exercise for which the circulation suffices. An exquisite illustration that even pronounced structural changes in the heart do not necessarily entail circulatory failure is contained in the recent report of Jokl and Suzman[3] of a marathon runner with mitral stenosis and aortic regurgitation who ran 26 miles in three hours and two minutes on a hot day, finished in good condition, and recovered rapidly.

THE TYPES OF CIRCULATORY FAILURE OR CARDINAL CIRCULATORY SYNDROMES

Various derangements may diminish the ability to accommodate blood flow to the needs of the body and thus lead to circulatory failure. In the following paragraphs the attempt will be made to classify these derangements in accord with the needs of the clinician, and thus subdivide the broad, collective concept of circulatory failure To the individual types of circulatory failure thus differentiated—which recur again and again, alone or in combination, in the various diseases affecting the circulation—the designation *cardinal circulatory syndromes*[1] may be applied.

THE CARDINAL CIRCULATORY SYNDROMES

Circulatory failure	Peripheral circulatory failure	Oligemic	
		Motor	
	Heart failure	Hyposystolic	Left-sided
			Right-sided
			Bilateral
		Hypodiastolic	Limitation of diastole
			Abbreviation of diastole

From the point of view of pathological physiology, the circulatory failures fall naturally, and indeed quite obviously, into two great groups: *heart failure* and *peripheral circulatory failure.* In heart failure the inadequate circulation is due to deficiency of the cardiac pump; in peripheral circulatory failure to derangements initiated in the peripheral vessels or circulating blood itself which entail a deficient venous return to the heart and consequently, despite the absence of cardiac weakness, inadequate cardiac output. Such

primary subdivision of circulatory failure into cardiac and peripheral types is not only natural from the "academic" standpoint of pathological physiology but is also feasible and extremely useful in clinical medicine; the cardiac and peripheral circulatory failures not only each have fundamentally similar clinical pictures, but the treatment of a patient with a failing circulation is primarily determined by whether the failure is of cardiac or peripheral origin.

In the case of *heart failure*, certain further subdivision is not only called for by clinical requirements, but can also be carried out in practice in the large majority of instances. First of all, corresponding to the physiologic division of the cardiac cycle into diastole and systole, those forms of cardiac insufficiency which are due to inadequate diastolic filling of the heart (*hypodiastolic failure*) are to be differentiated from the far more common ones in which the heart fills adequately but does not empty to the normal extent (*hyposystolic failure*).

Of the comparatively rare hypodiastolic failures, there are two main varieties, *viz*, those in which the *amplitude* of diastole is diminished by pericardial effusion or incarceration by a shrinking pericardium, and those in which the *duration* of diastole is shortened by paroxysmal tachycardia or other extreme acceleration in rate Hypodiastolic failure results in decreased cardiac output as well as engorgement of the systemic veins and, usually to a much less extent, of the lesser circulation. It tends to diminish the size of the heart because of the decreased filling.

Of the hyposystolic failures, which constitute the vast majority of instances of heart failure, there are likewise two fundamental categories, namely, *insufficiency of the left side of the heart*, characterized by engorgement of the pulmonary circuit, and *insufficiency of the right side of the heart*, marked by engorgement of the systemic veins. In each case, primarily ventricular and primarily auricular failure can usually be distinguished, but the type of aberration in circulatory dynamics is fundamentally similar. Left and right sided failure are often combined from the start. Hyposystolic failure tends to increase the size of the failing chamber, a phenomenon correlated with the deficient emptying.

In the primarily *peripheral circulatory failures* the derangement of the circulation is such that the amount of blood returning to the heart from the capillaries (venous return) is diminished, which entails *equal decrease in cardiac output. In consequence, the peripheral* circulatory failures are characterized by a depleted state of the large systemic veins with low venous pressure and a tendency to decrease in the size of the heart because of diminished diastolic filling. There are two general forms of peripheral circulatory failure, differentiated by the mechanism which produces the diminution in venous return: (1) The *oligemic form*, in which extravasation of either plasma or

whole blood decreases the circulating blood volume and thereby the venous return, and (2) the *motor form*, in which alterations in the state of contraction of the vessels lead to pooling of excessive quantities of blood in the periphery. Details of the pathogenesis of the oligemic and motor forms of peripheral circulatory failure are discussed in Chapter XXXII.

The cardinal circulatory syndromes depicted in the above schema constitute the elements of which the clinical picture of circulatory failure is compounded. Often, one of the cardinal circulatory syndromes is present in isolated form; thus, failure of the left side of the heart, even of severe degree, frequently remains uncomplicated for years in patients with essential hypertension. On the other hand, circulatory failure may be complex from the very start; for example, both left and right sided failure may develop simultaneously A very common sequence of events is for one of the cardinal circulatory syndromes to be present alone for a time, and then be complicated by another. The most common example is the addition of insufficiency of the right heart to pre-existent failure of the left heart. Such complication adds new symptoms to the clinical picture, although, on the other hand, some of the manifestations of the cardinal circulatory syndrome first present may be alleviated by the complication Thus, dyspnea and orthopnea present as a result of the pulmonary engorgement of left heart failure may be alleviated when the right heart weakens with consequent diminution in the blood content of the lungs. One cardinal circulatory syndrome may produce another; for example, peripheral circulatory failure due to hemorrhage or other cause may so diminish coronary flow as to entrain myocardial necrosis and consequent heart failure

Shock —The term shock does not appear in the above classification of circulatory failure. The reasons for this omission are discussed in Chapter XXXII There it will be brought out that the clinical picture so well known to every physician as shock may result from any of the forms of circulatory failure—either peripheral circulatory failure or heart failure—provided they sufficiently diminish the cardiac output, for shock is merely the symptom complex resulting from inadequate cardiac output. Thus, shock may result from the peripheral circulatory failure of hemorrhage, from the left sided heart failure of coronary thrombosis, from the right sided heart failure of pulmonary embolism, or from the hypodiastolic heart failure of hemopericardium. It will be noted that in the case of heart failure, shock is especially apt to result when the cardiac insufficiency is of abrupt onset so that compensatory mechanisms (notably increase in blood volume) have not yet developed to counteract the tendency to fall in cardiac output.

Harrison's Classification of Circulatory Failure.—In the brilliant monograph integrating his investigations on failure of the circula-

tion, which have contributed so importantly to clarification of the subject, Harrison[2] propounds the following classification of circulatory failure:

I. Forward failure.
  1. Forward failure of the peripheral vascular apparatus ("shock," "collapse")
    (a) Hematogenic ("secondary shock").
    (b) Neurogenic ("primary shock").
    (c) Vasogenic
  2. Forward failure of the heart.
    (a) Cardiac syncope
      (1) Neurogenic.
      (2) Myogenic.
    (b) Cardiac collapse
      (1) Due to tachycardia
      (2) Due to myocardial injury
      (3) Due to mechanical hindrance.
    (c) Sudden death (failure of the coronary circulation).

II Backward failure
  1 Failure of the left side of the heart
  2 Failure of the right side of the heart
  3 Failure of both sides of the heart

Harrison thus differentiates primarily between *forward failure* and *backward failure*, depending on whether the clinical picture results principally from diminished blood flow to the tissues or from passive engorgement of the circulation upstream to the failing chamber of the heart This differentiation of forward and backward failure serves a useful purpose in graphically expressing the form taken by the circulatory disturbance and the pathogenesis of the symptoms; only too often in the past, despite the therapeutic implications, clinicians have made little attempt to analyze the nature of the disturbance in circulatory dynamics underlying the symptoms of inadequate circulation

Wollheim's classification of circulatory failure on the basis of blood volume is discussed on page 73

The first part of this book is devoted to the individual manifestations of circulatory failure The next section is concerned with the clinical picture engendered by circulatory failure, primarily from the point of view of the cardinal circulatory syndromes involved The final section is apportioned to the treatment of patients with circulatory failure

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2 HARRISON: Failure of the Circulation, 2d ed, Baltimore, The Williams and Wilkins Company, 1939
3 JOKL and SUZMAN Jour Am Med Assn, 114, 176, 1940

CHAPTER II

THE CARDIAC OUTPUT

Perhaps the most fundamental of the circulatory variables is the volume of blood that passes in each unit of time through the capillaries of the greater and the lesser circulations. Control of this variable is the principal of the many mechanisms by which the ever-changing circulatory requirements of the organism are met. It is therefore not surprising that the relatively recent inauguration of quantitative studies of the minute volume has already led to significant advances in knowledge of circulatory physiology and pathology. Before discussing these studies, a few words concerning the sometimes confused terminology of the field may not be amiss

THE VOLUME OF CIRCULATION AND THE CARDIAC OUTPUT

The terms volume of circulation, minute volume of circulation, minute volume, rate of circulation, cardiac output, and minute volume of the heart are frequently used as synonyms. Grollman[18] prefers the term cardiac output because the others can be confused with the expressions circulating blood volume and velocity of blood flow. However, from a didactic point of view there is also objection to the use of "cardiac output," for it tends to perpetuate the antiquated point of view which lays all the emphasis on the activity of the heart as the determinant of the volume of circulation and ignores the primary rôle of the peripheral regulations of the volume of flow.

It is to be remembered that the terms cardiac output and volume of circulation are not always synonymous. Cardiac output designates the volume of blood expelled by either ventricle in a unit of time through a complete cross-section of the vascular bed, *i. e.*, either the pulmonary artery or the aorta proximal to the orifices of the coronary arteries. With perfectly functioning semilunar valves and no abnormal communication between the two sides of the heart, the cardiac output and the volume of circulation are equal. But in aortic insufficiency the output of the left ventricle is greater than the volume of circulation by the volume of regurgitated blood, and this may be very considerable (page 467). A discrepancy may also exist when there is a shunt between the two halves of the heart or a patent ductus arteriosus. The acetylene and the other gasometric methods now used almost exclusively in

clinical work measure the volume of blood flow through the lungs, *i. e.*, the volume of circulation and not necessarily the cardiac output. On the other hand, the roentgen method (page 34) measures the cardiac output and not necessarily the volume of circulation. In this book, both terms, cardiac output and volume of circulation, will be used, but the distinctions just mentioned are to be borne in mind.

REGULATION OF THE CARDIAC OUTPUT

The prime determinant of the volume of blood pumped by the heart is the oxidative metabolism. When oxygen consumption is high, as in exercise or Graves' disease, the cardiac output is elevated, while the reverse is true when the oxidations are diminished during rest or in myxedema. However, other factors also enter, so that the volume of circulation is not always strictly proportional to the oxygen consumption. Thus, Grollman has found that different forms of exercise may be accompanied by unequal cardiac output even though the oxygen consumption is the same; apparently, in some forms the venous return to the heart is more increased by the muscular movements. Grollman further observed that the cardiac output remained constant when the environmental temperature changed from 0° C. to 30° C., despite the fact that the oxygen consumption decreased from 330 to 240 cc. per minute. In hyperthyroidism the cardiac output may be increased proportionally more than is the metabolic rate and in hypothyroidism less (Chapter XXIX)

As will be seen in the succeeding chapters, the mechanisms through which the cardiac output is adapted to the metabolic and other needs are very complex and only imperfectly understood. However, it seems that this regulation is effected, in general, through the intermediacy of the venous return to the heart. Increase in venous return bears in itself the adequate stimulus for corresponding augmentation in cardiac work (Chapter XVIII) so that the greater volume of blood returning to the heart is ejected and the circulation maintained at the level dictated by metabolism As will be seen in Chapter XVIII, this accommodation to the venous return is effected through alterations in the output of the heart per stroke as well as in the rate. It appears probable that the cardiac nerves do not determine the output of the heart per minute, but function principally to regulate the fashion in which the total cardiac work is partitioned into strokes, *i. e.*, they serve to accommodate the rate of the heart to the work required of the organ (Hess[23])

This conception of the regulation of the cardiac output—dominant since the work of Starling though considered one-sided by Grollman—may be represented in broad schematic outline as follows, although of course in actuality innumerable factors participate.

Increment in metabolism→increased venous return→greater cardiac output.

How the greater venous return leads to corresponding augmentation of cardiac output will be discussed on page 300. Much remains to be learned about the mechanisms through which increase in metabolism elevates the venous return; these doubtless vary in different circumstances Physical exercise may be briefly discussed as an example.

Regulation of the Volume of Circulation During Exercise.—With the onset of the exercise, the arterioles dilate and many capillaries are opened up in the active muscles, so that the blood flow through these muscles is greatly increased. The result is that much more blood enters the veins from these active muscles than during rest. This increase in venous return from the active muscles is only partially neutralized by decrease in the venous return due to collateral vasoconstriction in the splanchnic and other inactive territories. At the same time the total circulating blood volume is increased by mobilization of blood from the depots (Chapter IV) into the active circulation, thus increasing considerably the venous return to the heart, and the contraction of the active muscles serves to squeeze the blood out of the contained veins toward the heart, likewise augmenting venous return The summation of these and doubtless other factors serves to return far more blood to the heart per minute than during rest In turn, this augmented venous return spurs the heart to increased output by mechanisms that will be discussed (page 302) and thus meets the demands of the elevated metabolism. It should be mentioned, however, that not all the circulatory adjustments during exercise are effected through the intermediacy of increased venous return. Thus, the initial acceleration of the pulse during exercise probably is not due to reflexes of the Bainbridge type (see page 295) initiated by increased venous pressure but is more likely of psychic origin (see Bainbridge[1] for evidence). Only some such explanation would account for Buchanan's[8] observation that the acceleration of the heart begins with the first beat after the onset of exercise.

Correlation of the Minute Volume and the Utilization of the Blood.—Increase in volume of circulation is not the only means by which the circulatory demands of heightened metabolism are met. If it were, the heart would be called upon in vigorous muscular exercise for an output that is probably beyond its capacity. Instead, the heart is spared by shifting a part of the burden to increased utilization, by means of greater arteriovenous differences, of the volume of blood that it does pump. This mechanism may again be illustrated by observations in muscular exercise. At rest, only about 30 per cent of the oxygen of the arterial blood is used in the tissues (Lindhard[33]), leaving a reserve of about 70 per cent of the

original arterial oxygen which remains in the mixed venous blood that returns to the right heart.* In vigorous muscular exercise, on the other hand, a much higher percentage of the arterial oxygen may be utilized by the tissues, especially if the individual is a trained athlete. Thus, in one of Christensen's[10] subjects, the arteriovenous oxygen difference at rest was 62 cc. per liter, while during the performance of 1080 kilogram meters of work per minute, the arteriovenous oxygen difference rose to 131 cc per liter, or more than double the value at rest. It would seem that the main factor in inducing the greater utilization of the blood in muscular exercise is the higher proportion of the total blood flow that passes through the active muscles as a result of the opening up of arterioles and capillaries in these tissues and the simultaneous collateral vasoconstriction in the inactive tissues. In the active muscles the oxygen in the tissues is used up more rapidly so that the concentration falls and the oxygen gradient between blood and tissue is greater, with the result that more oxygen diffuses from the blood Moreover, the greater acidity in the active territory so affects the dissociation curve of oxyhemoglobin that oxygen is more readily unloaded. Other factors that may be concerned in producing the more efficient utilization of the blood during muscular exercise are the greater capillary surface available for exchange and the higher local temperature

Increased cardiac output and more efficient utilization of the blood are thus intimately correlated in meeting the circulatory demands imposed by greater metabolism In the following, there will be frequent occasion to refer to this all-important correlation and its aberrations in disease.

MEASUREMENT OF THE CARDIAC OUTPUT

The measurement of the volume of circulation in man and the intact experimental animal is a goal toward which physiologists and clinicians have been striving for the past century; in fact, estimates based on the capacity of the chambers of the heart and the pulse rate were made much earlier But it is only within recent years that relatively satisfactory methods, affording results of at least the correct order and applicable in the clinic, have been devised As yet, however, these methods—apart from those involving entry into the right side of the heart, which are undesirable for clinical use—suffer from the limitation that their accuracy in conditions of severe pulmonary engorgement is open to some question

The technic of the methods for determining the volume of circulation will not be described here. For this, the reader is referred

* The proportion of the arterial oxygen that is utilized varies in the different organs Thus, Van Slyke *et al* [11] find that the blood in the renal vein of the dog is 85 per cent saturated with oxygen

to the splendid monograph of Grollman,[18] *in which will be found a* detailed account not only of his own fundamental contributions but also of the literature. Only the general principles of some methods, which are either practically important or theoretically interesting, will be mentioned. Following Grollman, these methods may be *discussed in three categories: (1) Physical methods; (2)* methods based on the Fick principle, (3) methods employing a foreign gas.

Physical Methods.—Meek and Eyster[40] developed an ingenious device for synchronizing roentgen exposures with the waves of the electrocardiogram. By this means they took pictures during *systole and diastole. The systolic and diastolic volumes of the* heart were calculated from the corresponding areas of the cardiac silhouette by Bardeen's formula. The difference between these volumes is the cardiac output per stroke. The accuracy of the calculation of the volume of the heart from the surface area would *seem questionable in pathological hearts. The technic is rather elaborate and the method appears to have found little application.* It is, however, of decided theoretical interest because it measures the actual cardiac output and not the volume of circulation, as do the gasometric methods If Meek and Eyster's method could be *developed to a sufficient degree of accuracy, the difference between* the result obtained and the volume of circulation determined by the acetylene method would reveal the amount of regurgitation in aortic insufficiency or the amount of a right-to-left shunt in abnormal communications between the two sides of the circulation.

Broemser and Ranke[7] have devised a method for calculating the volume of circulation from the cross-section of the aorta, the velocity of the pulse wave, certain blood pressure data, the duration of systole and diastole, and the density of the blood. The technic for use in humans is elaborated by Lauber and Przywara.[29] The method is laborious and certain of the underlying measurements questionable; Grollmann is therefore skeptical of its reliability. However, using Broemser and Ranke's formula, Bickenbach[5] found in 20 individuals with unimpaired circulation an average stroke volume of 64.5 cc. and a minute volume of 4.31 liters, results agreeing well with the acetylene method

Methods Based on the Fick Principle.—Fick[14] long ago pointed out that the following considerations afford a basis for the determination of the volume of circulation: All the blood pumped by the right ventricle traverses the pulmonary capillaries, where the gaseous exchanges with the alveolar air occur. Hence, if the amount of oxygen absorbed in a minute be divided by the difference in oxygen content between a liter of the blood of the pulmonary vein and a liter of that of the pulmonary artery, the result will be the number of liters of blood that pass through the lungs in that minute. Thus, if the arterial blood contains 190 cc. of oxygen per liter, the

mixed venous blood, 130 cc. per liter, and 240 cc. of oxygen are absorbed in a minute, the volume of blood that passes through the lungs in that minute is $\frac{240}{190 - 130} = 4$ liters. Similar calculations can be made for carbon dioxide. This calculation of the volume of circulation as the quotient of the volume of gas exchange through the lungs divided by the arteriovenous difference of the gas is known as the *Fick principle*, and has played a notable rôle in the development of the study of the volume of circulation.

The application of the Fick principle has rendered feasible the *direct* determination of the volume of circulation in man This was accomplished by Lauter,[30] Baumann,[3] Baumann and Grollman,[4] and McGuire and his associates,[41] who obtained the mixed venous blood by puncturing the right heart with a needle, the arterial blood by arterial puncture, and the oxygen consumption by the usual technic. Similar determinations were carried out by Klein,[26] who passed a catheter from a vein in the right arm into the right heart By this direct method, Baumann and Grollman found the volume of circulation in healthy individuals between 3 and 5 liters per minute. Calculated on the basis of the body surface, these values correspond to a "cardiac index" (page 38) of about 2 2 liters per square meter body surface per minute. Owing to the directness of the method, these are the most accurate measurements of the cardiac output which we possess, and the validity of other methods may be checked by comparison with them.

Unfortunately, these direct methods of measuring the volume of circulation by entering the right heart are not applicable to clinical work because of the risk involved For this reason, a considerable number of indirect methods of applying the Fick principle have been devised and used extensively. They include both carbon dioxide and oxygen methods, the former being the more popular for technical reasons Various procedures (*e g.*, that of Donal[15]) are adopted to obtain samples of the respired air corresponding in gas content to the arterial and mixed venous bloods. A detailed description of these methods is given by Grollman, who considers none of them entirely free from objections, although they may furnish comparative results of considerable value.

Methods Employing a Foreign Gas.—These methods are based on the principle that the amount of a foreign gas in the inspired air which is absorbed by the blood is proportional to the volume of blood flowing through the lungs, *i e*, the volume of circulation. The subject breathes from and into a bag containing a mixture of air and a foreign gas of appropriate and known solubility in blood. Successive samples of the mixture in the bag are taken and analyzed for their oxygen and foreign gas content The first of the samples is taken after the subject has rebreathed into the bag sufficiently

to ensure a homogeneous mixture throughout the lung-bag system which is in equilibrium with the blood in the pulmonary capillaries. The last of the samples must be taken before sufficient time has elapsed (about twenty-two seconds in health*) after the start of the rebreathing for blood containing the foreign gas to return to the lungs, for this would alter the rate of absorption of the gas from the lung-bag system. From the change in concentration of oxygen and the foreign gas in the successive samples, and knowledge of the solubility of the foreign gas in blood, one can calculate the volume of blood passing through the lungs that absorbs a liter of oxygen. This determination does not itself yield the volume of circulation of the individual at rest, for the breathing procedures necessary to obtain a homogeneous mixture in the lung-bag system alter the rate of circulation. But if the oxygen consumption of the individual at rest be determined in liters per minute by the usual procedure for basal metabolism, and this figure divided by the volume of blood passing through the lungs that absorbs a liter of oxygen, the result will be the number of liters of blood passing through the lungs of the resting individual per minute, *i. e*, the volume of circulation.

The first foreign gas to be employed extensively was *nitrous oxide*, introduced by Krogh and Lindhard.[28] Later, Henderson and Haggard[22] applied *ethyl iodide*, their procedure was greatly improved by Starr and Gamble.[47] However, various technical details militated against the general adoption of either of these gases.

More recently, Grollman has applied *acetylene* as the foreign gas. He points out that this gas possesses a number of properties which adapt it admirably to the purpose. Grollman finds that the solubility of acetylene in blood corresponds closely to that in water, so that the physical laws for the solubility of gases in fluids can be applied to acetylene in blood. Moreover, Baumann and Grollman[4] have shown by comparative study of the acetylene tensions in the alveolar air and arterial blood that the gas passes very rapidly through the alveolar walls, so that a very quick tensional equilibrium is attained

The acetylene procedure has largely displaced the other methods for the determination of the volume of circulation, being the technic applied in most recent studies. It does, indeed, seem to be the most generally useful and accurate method for the measurement of the volume of circulation at present available. Rigorous proof of the accuracy of the aceytlene method in the absence of severe pul-

* Recently, Gladstone[16] has brought forward evidence that because of the hyperventilation during the rebreathing procedure, blood containing the foreign gas may return to the lungs within ten seconds To avoid an error due to such recirculation, Gladstone has modified the acetylene method so that it is terminated within ten seconds However, it appears that the error due to recirculation is not significant unless the circulation is much accelerated, and that even then the error may not be considerable (see page 37)

monary engorgement was furnished by Baumann and Grollman,[4] who showed that the values obtained correspond very closely to those obtained by the direct Fick method of puncturing the right heart and an artery (page 35). Only in two instances—one with aortic regurgitation and another with phenobarbital poisoning (apparently unconscious)—were there considerable discrepancies with the direct method. However, this series apparently included no instances of severe cardiac failure with pulmonary engorgement. McMichael[23] estimates the standard error of one determination by the acetylene method as 6 4 per cent and of the average of two determinations as 4 5 per cent.

The limitations of the aceytlene method are discussed in detail by Grollman. The period during which the gas is breathed should be less than the circulation time of the blood, for the return to the lungs of blood containing notable amounts of acetylene would introduce a significant error (the minute amount of acetylene that quickly returns from the coronary circulation causes only a small error). In individuals with normal vital capacity and a circulation time that is not greatly accelerated, the amount of acetylene returning is probably too small to be significant, and moreover the consequent small error is partly neutralized by a compensating error resulting from the acceleration of the circulation by the deep breathing. But Grollman finds that when the velocity of blood flow is markedly accelerated—as in severe thyrotoxicosis or exercise with a volume of blood flow in excess of 10 liters per minute—the possibility of error due to recirculation has to be borne in mind Nevertheless, Grollman obtained a close check with the direct method in an instance of Graves' disease with the greatly increased volume of circulation of 11.8 liters per minute. Christensen[10] obtained excellent results with the acetylene method in vigorous exercise, the return of minute amounts of acetylene during the rebreathing period apparently introducing no notable error.

The question of the applicability of the acetylene methods to patients with heart failure is an important one. That a tensional equilibrium between alveolar air and blood is attained in the pulmonary engorgement of heart failure was established by Baumann and Grollman, who found that in two such cases the acetylene tensions of the arterial blood and alveolar air were almost identical. It might be anticipated that in severe pulmonary engorgement the changes in the lungs and the diminished vital capacity would delay the attainment of a homogeneous mixture in the lung-bag system and equilibrium between alveoli and blood until past the time when recirculation occurs and thus render the acetylene method invalid. However, Grollman, Friedman, Clark and Harrison[19] showed that this error can generally be avoided by taking advantage of the fact that, because of the slower velocity of blood flow in heart

failure, recirculation usually does not become significant in less than thirty seconds. This enables the first gas sample to be taken twenty seconds after the start of the rebreathing, which allows time for homogeneous mixture in the lung-bag system. Subsequent samples are taken at twenty-five and thirty seconds, and if the value calculated from the twenty- and twenty-five-second samples agrees with that from the twenty-five- and thirty-second samples, the determinations may be taken as reliable. McGuire and his associates[35] have compared the results obtained by this technic with those of the direct Fick method (puncture of the right heart) in 6 patients with severe heart failure and pulmonary engorgement. There was practical identity in 2 of the cases, but in the others the acetylene method, while agreeing qualitatively with the direct procedure, yielded lower absolute values

It would appear that the cardiac output can be measured by the acetylene method in all but severe pulmonary engorgement in which the vital capacity is very low. In severe emphysema the acetylene method may be inapplicable, for Baumann and Grollman found a difference of 10 per cent between the acetylene contents of the sample from the lung-bag system and the arterial blood; apparently, a homogeneous mixture had not been attained because of the defect in respiratory mechanics.

NORMAL VALUES AND VARIATIONS OF THE CARDIAC OUTPUT

It was mentioned above that Baumann and Grollman found by a direct Fick method, apparently devoid of any considerable source of error, that the volume of circulation in health is between 3 and 5 liters per minute, or about 2.2 liters per square meter of body surface per minute. The results of the acetylene method are the same. In 50 healthy young adults in the basal state, Grollman found the volume of circulation to be between 2.96 and 4.61 liters per minute. This considerable variation is due to differences in the size of the individuals. Lindhard[33] showed that, in a general way, the volume of circulation is proportional to the oxidative metabolism. Inasmuch as the latter varies with the body surface, it might be expected that this would also be true of the volume of circulation. Grollman has shown this to be the case. He finds with the acetylene method that the volume of circulation of healthy adults is 2.2+ 0.3 liters per square meter body surface per minute, the average deviation from the mean being only 6.4 per cent. Because of this close proportionality of the volume of circulation to the body surface, Grollman uses the term *cardiac index* to designate the volume of circulation for each square meter of body surface per minute. Determinations by Galle[15] with the nitrous oxide method indicate, as would be expected, that the cardiac index is higher in children than in

adults. In adults between forty and eighty years, Lewis[32] found a very small decrease in cardiac index with advancing years. This corresponded to a decline in oxygen consumption, the arteriovenous oxygen difference changing little.

The disputed question of the effect of posture on the volume of circulation is discussed on page 176.

A number of physiological circumstances affect the volume of circulation As would be expected, it has been found that emotion, muscular exercise, the ingestion of food, or any other moment tending to increase metabolism is accompanied by augmentation in the volume of circulation. The relation of these and many other factors to the volume of circulation has been investigated by Grollman, to whose monograph the reader is referred. He found that environmental temperature has little effect on the volume of circulation below 30° C, but that above this the cardiac output rises with greater temperature. Grollman showed that residence on Pike's Peak or experimental anoxemia of like degree increases the volume of circulation, but that this occurs only after a certain period of time, which he interprets as indicating that the increased cardiac output is not due directly to the anoxemia but is a secondary result of other adaptations of the organism. With very low oxygen tensions of the inspired air, corresponding to below about 11 6 per cent of oxygen, Grollman found an immediate increase in cardiac output. He detected no definite correlation of the volume of circulation with the menstrual cycle.

As might be expected, variations in metabolic rate tend to call forth corresponding alterations in cardiac output in disease as well as health. This is best illustrated by the great increase in volume of circulation in hyperthyroidism and decrease in hypothyroidism. There is also evidence that the increased metabolism of fever likewise augments the volume of circulation. Another pathological moment that tends to occasion compensatory increase in cardiac output is the decreased oxygen-carrying capacity of the blood in anemia. These and other pathological variations in volume of circulation will be described in the sections on the individual disturbances In the next paragraphs, only the effects of circulatory failure as such on the volume of circulation will be discussed

THE VOLUME OF CIRCULATION IN HEART FAILURE

It seems a reasonable assumption that heart failure should *tend* to diminish the volume of circulation from the level that would be maintained at the same metabolism with unimpaired circulatory apparatus. If the limitation implied by the word "tend" be borne in mind, this assumption, long made by clinicians, has been established by recent investigations. The vast majority of individuals

with heart failure have a diminished cardiac output. But in exceptional cases with definite symptoms of heart failure, this tendency to decrease in cardiac output is overcome by compensatory mechanisms and the volume of circulation maintained at the same level as when symptoms of heart failure are absent The state of affairs is analogous to that of the patient with renal disease who cannot elaborate a urine of high concentration, but nevertheless has no nitrogen retention because of compensatory polyuria

The pioneer observations on the volume of circulation in heart disease were made by Plesch.[43] Using a method of questionable accuracy based on the Fick principle with oxygen, he measured the minute volume in 7 patients with cardiac disease In 6 of these, the minute volume was within normal limits; in the other, it was high, but this may have been due to accompanying severe anemia. Since all of Plesch's patients were well compensated, his findings threw no light on the problem of the minute volume in heart failure. Similarly, Newburgh and Means,[42] using the nitrous oxide method, found in a patient with compensated mitral and aortic defects that the minute volume, both at rest and after exercise, did not deviate essentially from the normal.

The first observations of the volume of circulation in heart failure were carried out by Lundsgaard.[34] He used the nitrous oxide method of Krogh and Lindhard While Grollman states that, in the presence of pulmonary engorgement, this method gives absolute values which are probably too high, nevertheless Lundsgaard's figures are doubtless of comparative value and show at least the direction of changes in minute volume. In 5 of the 6 decompensated cases of valvular disease which he studied, the volume of circulation was depressed very markedly, while the individual with a minute volume approximating the normal was only slightly decompensated. In some of Lundsgaard's patients, the cardiac output was well under half the normal The stroke volume was decreased relatively more than the minute volume However, Lundsgaard noted that no proportionality existed between the depression in volume of circulation and the severity of the clinical manifestations of cardiac failure. In fact, Lundsgaard found that 2 of 4 cases of valvular disease which were clinically compensated had subnormal cardiac outputs.

Following the work of Lundsgaard, numerous studies of the minute volume in heart failure were carried out They include investigations with methods based on the Fick principle using either carbon dioxide or oxygen (Meakins, Dautrebande and Fetter;[39] Eppinger, Kisch, Schwarz and von Papp,[12] Smith, Walker and Alt;[45] Ewig and Hinsberg[13]); with ethyl iodide methods (Henderson and Haggard,[22] Ringer and Altschule;[44] Mobitz;[41] Kininmonth,[25] Lauter and Baumann[31] and Starr, Collins and Wood[46]

with a greatly improved technic); with the original acetylene method (Stewart and Cohn;[49] Kroetz;[27] Bansi and Grosscurth;[2] Grassmann and Herzog,[17] Kerkhof[24]); and with the concentration curve of injected dye (Hamilton, Moore, Kinsman and Sperling[20]). Except for the acetylene and the improved ethyl iodide methods in relatively well-compensated patients the accuracy of *absolute* values obtained by these methods is open to question. Even the original acetylene method without the modifications necessitated by diminished vital capacity (page 37) is not reliable in heart failure. However, the general direction of the changes in cardiac output is probably correct in most cases

Except Eppinger[12] and his associates* all these investigators find that when the cardiac output is changed by heart failure, which is not always the case, it is diminished However, a number of investigators have found that there are cases with definite symptoms of heart failure in which the cardiac output at rest is within the limits of normal. Moreover while the cardiac output may fall as the symptoms of heart failure become worse and rise with improvement (see below), there are also instances in which the restoration of compensation is accompanied by little change in the volume of circulation. In severe heart failure, the fall in cardiac output may be very striking. Thus in a decompensated patient with mitral stenosis and auricular fibrillation, Grassmann and Herzog found the minute volume by the acetylene method 42 per cent below the estimated normal. Doubtless, the depression of the cardiac output may be even greater than this in extreme failure in which present methods for measurement of the volume of circulation cannot be applied Almost always, with the exception of cases with heart block, tachycardia results in the stroke volume being lowered more than the minute volume In the above-mentioned case of Grassmann and Herzog, the stroke volume was at times as low as 14 cc, a systolic discharge of the order of one-quarter the normal.

Because of technical inadequacies, the clinical studies thus far cited left much room for doubt concerning the effect of heart failure on the volume of circulation. To a considerable extent, this has been cleared up by the splendid investigations of Harrison, Friedman, Clark and Resnik,[21] who have obtained valuable data regarding the volume of circulation in heart failure. As mentioned above, these investigators and Grollman have modified the acetylene

* In detailed investigations using a method based on the Fick principle, Eppinger and his co-workers found that the cardiac output is sometimes increased over the normal value, especially during attacks of cardiac asthma These observations are diametrically the opposite of those made by all other investigators and do not accord with what one would anticipate from the clinical picture, as pointed out by Grollman, they are doubtless the result of technical inadequacies of the method employed for the determination of the cardiac output.

method so that it appears to afford reliable results with even considerable degrees of heart failure. Harrison and his associates studied 27 cardiac patients who were free from symptoms at rest and 19 with congestive failure; 15 subjects were studied in both conditions. They summarize their findings as follows:

"The cardiac output per minute of patients with congestive heart failure is usually from 10 to 30 per cent less than that of normal subjects but may be within the normal range. Patients without circulatory disorders may have an equally low cardiac output. The level of the cardiac output per minute, whether considered as such or in relation to the metabolic rate, bears no relation to the presence or absence of congestive failure for.

"1. The range and the average values of the cardiac output are similar for compensated and decompensated patients.

"2. In a given individual clinical improvement and disappearance of congestive phenomena may be associated with an increase, a decrease or no change in this function In general, the output of the heart per beat tends to be somewhat less during congestive failure."

More recent investigations confirm the lack of close parallelism between the intensity of symptoms of heart failure and diminution in cardiac output. They do show, however, that the cardiac output is decreased in the vast majority of instances of cardiac insufficiency. Thus, McGuire and his associates[36] found the cardiac output subnormal in 19 of 20 patients with heart failure; the average cardiac output was 1 52 liters per square meter body surface per minute as contrasted with 2 16 liters in the controls. Stewart[48] found that in valvular disease failure results in decreased volume of circulation; with recovery the cardiac output increases but usually does not regain the level maintained before the heart failed.

As would be anticipated, arrhythmia tends to lower the cardiac output. Kerkhof[24] and Stewart[50] and his associates found the cardiac output diminished in auricular fibrillation, auricular flutter, and paroxysmal tachycardia. Stewart also observed that the minute volume is generally lessened in heart block although the stroke volume is augmented.

Effect of Exercise on the Minute Volume in Heart Disease.—Many individuals with compensated cardiac strain are able to perform vigorous exercise. It is therefore not surprising that, as mentioned above, Newburgh and Means observed that a patient with compensated aortic and mitral disease increased his cardiac output in response to graded muscular work much as did a normal subject. Similarly, Smith, Walker and Alt[45] found that when 7 patients with compensated heart disease (chronic rheumatic valvular defects, subacute rheumatic fever, "chronic myocarditis," and complete heart block) were subjected to moderate exercise on

the bicycle ergometer the cardiac output was augmented essentially as in normals.

Perhaps more important is the question of the effect of exercise on the cardiac output in heart failure. It is to be anticipated that even in those cases of cardiac failure in which the volume of circulation at rest is within normal limits, the patient will be unable to increase his cardiac output on exercise as much as he could when healthy. In accord with this conception McGuire and his associates[37] found with the three-sample acetylene method that an exercise which augmented the cardiac output of normals by an average of 2.07 liters per minute, produced an increase of 1.21 liters in patients with compensated heart disease and only 0.75 liter in decompensation.

The minute volume of cardiac patients in the recovery period after exercise has been studied by Bansi and Grosscurth.[2] They found that in well-compensated heart disease the cardiac output increases with the oxygen consumption. But they made the further observation that after the exertion is over, the volume of circulation does not return to its resting value as rapidly as in health. Thus, for example, while the minute volume of their normals dropped to its resting value within six minutes after cessation of exercise this took about sixteen minutes in one of the cardiac patients. This prolongation of the post-exertional increase in minute volume in fairly well-compensated heart disease was found by Bansi and Grosscurth to accompany a corresponding protraction of the increased oxygen consumption due to the exercise. In other words, even in cases with very little clinical evidence of heart failure, more of a "circulatory debt" and of an "oxygen debt" in the sense of Hill are accumulated during exercise than does a healthy person. This prolongation of the post-exertional increase in oxygen consumption would seem good evidence that, even though the minute volume at rest was normal, during exercise the volume of circulation was not increased to as high a level as in an individual with intact circulatory apparatus. In neuroses with circulatory manifestations, Bansi and Grosscurth did not observe prolongation of the recovery period. They therefore believe that the protraction of the post-exertional period of increased cardiac output may be a sensitive indicator of minimal degrees of heart failure, which are not evident from the clinical findings.

The Arteriovenous Oxygen Difference in Heart Failure.—Information regarding the cardiac output may also be derived indirectly from the arteriovenous oxygen difference. Since the basal metabolism (oxygen consumption) of patients with heart failure is either normal or more often increased, one would anticipate that decrease in cardiac output would be manifested by an increase in the difference between the oxygen contents of the arterial and the mixed

venous blood entering the right auricle. In the acetylene method for measuring the cardiac output, the arteriovenous oxygen difference is determined; normally, it is about 60 cc. per liter. In very severe heart failure, Grassmann and Herzog[17] and Harrison[21] and his associates found that the arteriovenous oxygen difference may exceed 130 cc. per liter, a figure which represents the utilization of more than twice the normal proportion of the oxygen of the arterial blood. However, Harrison and his school have shown that there is no close proportionality between the severity of heart failure and the arteriovenous difference at rest, and that the former may be accompanied by a normal arteriovenous difference, which may not change during improvement. When present, the greater arteriovenous oxygen (and carbon dioxide) difference subserves a compensatory function in at least partially atoning for the decrease in volume of blood flow. But it presumably carries with it the inherent disadvantage that the tissues are supplied with oxygen at a lower average tension even though the oxygen saturation of the arterial blood is normal

RELATIONS OF THE CARDIAC OUTPUT TO THE CLINICAL EVIDENCES OF HEART FAILURE

The investigations cited in the foregoing show that heart failure results in actual or potential diminution in the volume of circulation. The word *potential* is introduced because in slight or moderate heart failure, even with symptoms at rest, the volume of circulation at rest may be within the limits of normal, diminution in cardiac output appears only when the strain on the circulatory apparatus is increased by exercise, and then only in the relative sense that the volume of circulation is not augmented as much as normally.

Nevertheless, *diminution in the volume of circulation is not to be regarded as the complete dynamic substratum of the clinical concept of heart failure; it is not to be thought that all the clinical manifestations of heart failure are consequences of a subnormal volume of blood flow.* This is immediately indicated by the fact—already pointed out in the first studies on cardiac output in heart failure by Lundsgaard but best established by the detailed studies of Harrison and his school—that there is no close parallelism between the intensity of the clinical manifestations of heart failure and the volume of circulation Harrison *et al.*,[21] Ewig and Hinsberg,[13] Grassmann and Herzog,[17] and others have found that a patient with heart failure may improve and such manifestations as dyspnea and edema clear up even through there has been no change in cardiac output. Some of Ewig and Hinsberg's hypertensive patients with heart failure had a larger cardiac output than others who were well compensated. In mitral stenosis, also, Grassmann and Herzog observed a

small volume of circulation in the absence of symptoms of heart failure. Various observers have found that Graves' disease may be accompanied by such symptoms of heart failure as swelling of the liver, edema about the ankles, and cyanosis despite a minute volume that is well *above* normal. It is doubtless true that in such cases, because of the increased oxygen consumption, the minute volume would be even higher if the heart were not insufficient, *i. e.*, there is a relative diminution in the cardiac output below the level called for by its usual dictator, the respiratory metabolism. Nevertheless, these cases are important in that they demonstrate that the clinical picture of heart failure may be present despite a volume of circulation above the normal

Because of the usual tachycardia, the correspondence between diminution in stroke volume and the intensity of the clinical manifestations of heart failure is closer than between the latter and the minute volume. But even in the case of the stroke volume the inverse parallelism is by no means invariable

It thus seems clear, as especially Harrison has emphasized, that heart failure does not produce its clinical manifestations—the symptoms and signs of decompensation—solely through diminution in the volume of circulation. Indeed, it will be seen in the analysis of such classical symptoms of cardiac failure as dyspnea, cyanosis, and edema, that lessened cardiac output is only one of the factors in their pathogenesis, and one which is often absent or of only secondary significance. As will be seen in the following chapters, it is usually only in the terminal stages of heart failure, or when the latter is of very sudden inception (as in coronary thrombosis or paroxysmal tachycardia), that there appear manifestations of a deficient volume of blood flow through the organs at rest Only in some instances of acute heart failure, notably in coronary thrombosis, does it appear that the major part of the clinical picture results from inadequate blood flow to the organs due to decreased cardiac output.

The lack of parallelism between the intensity of the symptoms of most instances of heart failure and the volume of circulation is largely due to the operation of two varieties of compensatory mechanisms: (1) Mechanisms tending to maintain the cardiac output despite functional impairment of the heart, and (2) mechanisms increasing the utilization of the cardiac output when the latter is diminished. These mechanisms will be discussed in detail in later chapters, but may be briefly outlined here

Factors Tending to Elevate Cardiac Output in Heart Failure.—The primary characteristic of heart failure of any considerable duration is engorgement of the vascular bed upstream to the functionally impaired chamber of the heart. In left-sided failure the pulmonary circuit is engorged, in right-sided failure the venæ

cavæ and their tributaries. The pressure in the engorged segment of the vascular bed is increased. In accord with Starling's law of the heart, this increase in tension increases the diastolic filling of the failing chamber and thereby augments the work performed by this chamber in the succeeding systole. Through this mechanism the output of the failing chamber is elevated and may reach the normal level. But the engorgement of the stream bed upstream to the failing chamber which tends to raise the output has, at the same time, deleterious effects which result in the classical symptoms of heart failure. It will be seen in later chapters that the most important factor in the production of cardiac dyspnea is the pulmonary engorgement just described, and that cardiac edema is due primarily to engorgement of the systemic veins It is thus clear why there is no proportionality between the symptoms of heart failure and the cardiac output: *the very change in the distribution of blood which tends to maintain the cardiac output calls forth some of the cardinal symptoms of heart failure.*

More Efficient Utilization of the Cardiac Output.—When the cardiac output is decreased, there are two main mechanisms which tend to bring about more efficient utilization of the smaller volume of circulation. The first of these is the increased arteriovenous oxygen and carbon dioxide differences already described; presumably, there are similar increases in the arteriovenous differences of the other substances that are exchanged between blood and tissues As a result of the greater arteriovenous difference each cubic centimeter of blood pumped by the heart delivers a larger volume of oxygen to the tissues than normally, sometimes twice as much The second mechanism in question is the diversion, by vasoconstriction in inactive or less active organs, of a higher proportion of the cardiac output to the organs where it is most needed. There is experimental proof that this mechanism functions when the cardiac output is diminished by various procedures (page 631), and it would seem altogether likely that the same is true when diminution in cardiac output is due to heart failure. Such a mechanism would explain, for example, the pronounced coldness and cyanosis of the hands in some patients with mitral stenosis who have neither systemic venous engorgement nor notable dyspnea. As in the case of other bodily functions, the volume of circulation in health doubtless possesses a large factor of safety—a "luxus" volume of circulation, if we may so term it—which can be encroached upon considerably before symptoms appear.

Peripheral Circulatory Failure.—I am not aware of measurements of the *cardiac output* in human peripheral circulatory failure. But the clinical manifestations leave no doubt that the volume of circulation is greatly decreased, and this is substantiated by the findings in experimental shock. Blalock[6] showed that the volume of

circulation is decreased in shock produced by trauma, hemorrhage, or the injection of histamine, and Burch and Harrison[9] that the same is true when circulatory failure results from spinal anesthesia. These investigators found that in traumatic and hemorrhagic shock the decrease in cardiac output precedes the fall in arterial pressure, while the reverse is true in the experiments with histamine and spinal anesthesia. Apparently in trauma and hemorrhage vasoconstriction is able to maintain the arterial pressure despite a considerable fall in cardiac output due to decrease in circulating blood volume (page 631), while histamine and spinal anesthesia produce an initial vasodilatation.

The evidence seems adequate (cf Chapter XXXI) that, contrary to chronic heart failure, the clinical manifestations of peripheral circulatory failure are due almost entirely to decreased cardiac output with resultant inadequate perfusion of the organs

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CHAPTER III

THE VELOCITY OF BLOOD FLOW

Unless the circulating blood volume is correspondingly diminished, decrease in cardiac output entails retardation of the speed at which the blood circulates This slowing of blood flow participates in the production of many of the symptoms of heart failure. For this reason, the velocity of blood flow has been studied quite extensively in the short time since methods for its estimation in man have been devised The attempt has also been made to use the circulation time as an indication of the presence and degree of circulatory insufficiency. All these matters are discussed in detail in the splendid monograph of Blumgart.[3]

The speed with which the blood flows changes continuously as it makes its circuit. This alteration in velocity of blood flow is—considering the entire cross-section of the vascular bed—determined primarily by the hydrodynamic principle that the speed of a fluid column varies inversely with its cross-section. The architecture of the vascular tree is such that its cross-section increases progressively from the aorta to the capillaries, and then diminishes in similar continuous fashion from the capillaries to the venæ cavæ. The changes in cross-section are of enormous degree and the attendant variations in velocity of flow are of correspondingly formidable magnitude. Measurements of the velocity of flow in dogs by Burton-Opitz[5] and other investigators quoted by Wiggers[23] have afforded results of the following order· 240 mm. per second in the carotid artery, 1 mm. per second in the capillaries, and 150 mm. per second in the jugular vein. The velocity in the large veins is slower than in the corresponding arteries because of the greater cross-section of the former

Unfortunately, technical considerations have as yet prevented the carrying out of such direct measurements of the velocity of blood flow in man. It has therefore been necessary to resort to the "circulation time" as a clinical measure of the velocity of blood flow.

THE CIRCULATION TIME AND ITS MEASUREMENT IN MAN

By the circulation time is understood the time necessary for the blood to pass from one point of the vascular system to another, *i. e.*, the circulation time varies inversely as the average velocity of blood flow for the stretch in question. Such measurements were first made by Hering,[9] who injected potassium ferrocyanide into

one jugular vein of a horse and determined by the time of appearance of the Prussian blue reaction that the blood took twenty-six and two-tenths seconds to reach the other jugular vein. The same method was applied to man by Koch[11] in 1922. He injected a solution of fluorescin into an antecubital vein and by withdrawing successive specimens of blood from the other antecubital vein determined the time required for the substance to pass from one arm vein to the other. Koch found that in healthy adults the arm-to-arm circulation time varies between twelve and twenty-six seconds, with an average of about twenty seconds, and tends to be less in the young.

Notable advances have been made by Blumgart[3] and his associates, who have introduced the use of the active deposite of radium (radium C) for the measurement of the circulation time. They inject radium C into an antecubital vein and by means of a suitable detecting device observe the time required for the radium deposit to reach the right heart (arm-to-heart time) and further the time required for the substance to travel from the right heart to the arteries of the arm. Blumgart terms the latter interval the "crude pulmonary circulation time" It includes not only the time required for the blood to traverse the pulmonary circuit but also that consumed in the passage from the left heart to the brachial artery. However, the latter is so brief that for practical purposes the crude pulmonary circulation time may be considered to provide an adequate estimate of the pulmonary circulation time. Blumgart and Weiss[4] have determined the actual pulmonary circulation time by applying a standard correction based on other measurements.

With the radium method, Blumgart and Weiss found that in health the circulation time from an antecubital vein to the opposite antecubital arteries varies from twelve to twenty-four seconds in different individuals, with an average of eighteen seconds. The arm-to-heart time is between two and fourteen seconds, with an average of six and six-tenth seconds They find the pulmonary circulation time to vary between five and seventeen seconds, the average being ten and eight-tenth seconds But in the same subject Blumgart and Weiss have determined that the pulmonary circulation time is much less variable; successive measurements have an average deviation of only two seconds and a maximum variation of three and a half seconds.

Clinical Methods for the Measurement of the Circulation Time.—The apparatus required for the radium method precludes its general application For this reason, a number of other substances have been used for the clinical measurement of the circulation time.

Histamine.—Weiss, Robb and Blumgart[22] inject into an antecubital vein 1 to 5000 or 1 to 10,000 solution of histamine phosphate in amount equal to 0.001 mg. per kilogram of body weight. The

arrival of the histamine in the minute vessels of the face is signalled by flushing of the face, which is generally corroborated by a peculiar metallic taste in the tongue Weiss *et al.* found that the arm-to-face circulation time by the histamine method averages twenty-four seconds in health. Unfortunately, the injection of histamine in patients with circulatory failure is often followed by severe reactions, consisting principally in violent dyspnea, like an attack of cardiac asthma. Violent headache may follow. For these reasons, *histamine has been largely abandoned in favor of the* substances mentioned below.

Sodium Dehydrocholate (Decholin).—This substance was introduced by Winternitz, Deutsch and Bruell,[24] and extensively applied by Tarr, Oppenheimer and Sager[17] in various pathological states. Five cc of a 20 per cent solution are injected into an antecubital vein, and the arrival of the substance in the capillaries of the tongue is signalled by a bitter taste With this method, Tarr, Oppenheimer and Sager found the arm-to-tongue circulation time in health to *vary between ten and sixteen seconds.*

Sodium Cyanide.—Robb and Weiss[15] have applied the stimulation of respiration by sodium cyanide as an objective method of measuring the circulation time They use a 2 per cent aqueous solution of sodium cyanide, the optimum dosage being about 0 11 mg of sodium cyanide, per kilogram of body weight for antecubital injection; for injections into the jugular vein two-thirds of this dosage was used, and for injection into a foot vein one and a half times the antecubital dosage. The signal reaction is a sudden deepening of respiration, which can be observed directly or recorded graphically. Robb and Weiss bring evidence that the deepening of respiration is due to stimulation of the carotid sinus by the sodium cyanide, so that the method measures the arm-to-carotid circulation time. In normal subjects, they found that the arm-to-carotid time varies between nine and twenty-one seconds, with an average of fifteen and six-tenth seconds, the average foot-to-carotid time was twenty-seven and seven-tenth seconds.

By mixing sodium cyanide with the solution used by Spier, Wright and Saylor (page 53), Kvale and Allen[12] found that the cyanide circulation time is longer than that obtained with the other solution I have also often found that the circulation time indicated by saccharin is less than that with sodium cyanide. While the sodium cyanide method has the advantage of being objective, it is thus clear that the subjective methods afford a closer approximation to the actual circulation time

Saccharin.—This substance has been used by Fishberg, Hitzig and King[6] for the measurement of the arm-to-tongue circulation time. Two and a half grams of soluble saccharin (Merck) is dissolved by heating in 2 cc. of sterile distilled water. It is important

that the heating be only just sufficient to dissolve the saccharin, else sufficient evaporation will occur to result in recrystallization. The solution is taken up in a 5-cc. syringe attached to a 19-gauge needle and allowed to cool spontaneously to body temperature. The saccharin solution is obtainable in ampoules, which greatly facilitates the test. The patient reclines in bed in a position which is as nearly flat as comfortable. He is instructed to relax and not to hold his breath following the insertion of the needle. He is also told that he will experience a sweet taste, which he should announce immediately The arm is supported on a pillow so that the vein chosen is approximately level with the heart. A tourniquet is applied just before the insertion of the needle into a large antecubital vein and removed as soon as the needle is in the vein. After waiting about a minute for any circulatory disturbance consequent on the venepuncture and application of the tourniquet to subside, the injection is performed as *rapidly* as feasible. The importance of rapid injection is to be stressed. The time elapsing between the injection and the perception of the sweet taste is recorded with a stop-watch. The subject usually describes the sweet taste as passing with great rapidity from the base to the tip of the tongue and quickly diminishing.

By this method, the arm-to-tongue circulation time in health is between nine and sixteen seconds. I have now used the saccharin method for over six years, and have found it of great value in the clinical study of circulatory failure. A disadvantage of the method is that occasionally local venous thrombosis results; the frequency of this is less the more skilfully the injection is performed but sometimes, especially in patients with venous engorgement, it is unavoidable Failure to allow the solution to cool almost to body temperature also seems to favor thrombosis. Pain along the course of the brachial vein is not rare, but is not severe and soon passes away. There is no constitutional reaction to the injection of the saccharin, which seems to be entirely innocuous in the dosage of 2 5 grams.

Ether.—Hitzig[3] has introduced the injection of ether as a measure of the arm-to-lung circulation time. Five minims of ether mixed with an equal volume of physiological solution of sodium chloride is injected into an antecubital vein, and the time elapsing until the ether vapor in the expired air is perceived by the subject and generally also by an observer is noted. The interval is a measure of the circulation time between the antecubital vein and the arterial capillaries of the lung, which, in health, varies between four and eight seconds. Normally, the "ether time" is about one-half the "saccharin time," but in heart failure this relation may be disturbed and thereby yield information regarding the type of circulatory failure which will be described below.

Various other substances have been used for the measurement of the circulation time. Among them are carbon dioxide (Gubner, *et al.*[7]), magnesium sulphate (Bernstein and Simkins[2]), and calcium gluconate (Wall[21]).

Circulation Time of Different Circuits.—Spier, Wright and Saylor[16] have recently introduced a procedure for the coincident determination of the circulation time from the antecubital vein to the tongue, each hand, and each foot. They inject 2 cc of a solution containing 42 grams of magnesium sulphate, 16 grams of calcium gluconate, 0 9 gram of sodium chloride, and 1 mg. of copper sulphate in 100 cc. of distilled water. The arrival of the solution at the points in question is signalled by a sensation of heat. The average circulation time to the tongue is fourteen and six-tenth seconds, to the hands twenty-six seconds, and to the feet twenty-eight seconds, but there are considerable normal variations from the average. Further data indicating the value of the method in the study of peripheral vascular disease are to be awaited; Spier and his associates found a prolongation of the circulation time to the feet in Raynaud's syndrome, and Kvale and Allen[11] in thromboangiitis obliterans and arteriosclerosis obliterans.

Significance of Injection Methods for Determining the Circulation Time.—The injection methods for investigating the circulation time determine the time that it takes the *fastest* portion of the blood stream to reach the point of detection from the site of injection. It has therefore been objected that the circulation time thus determined yields no information as to the *average* velocity of blood flow. It is true that the axial portion of a fluid column may flow much more rapidly than the peripheral portions (twice as fast according to von Kries[20] and Tigerstedt[19]). However, it was shown by von Kries that the maximum velocity of flow is a function of the average velocity of flow Moreover, as pointed out by Blumgart,[3] in the frequently branching circulation with the inevitable lateral stresses exerted on the blood column at each branching, the same quantum of blood cannot remain long in the axial stream Further evidence that the injection methods of determining the circulation time actually measure the velocity of blood flow is supported by the observation that in the same individual there is a relatively constant difference between the arm-to-tongue and foot-to-tongue circulation times (Robb and Weiss,[14] personal observations). Additional evidence that the circulation time as measured by the injection methods affords an accurate index of the average velocity of blood flow is given in Blumgart's[3] monograph

Relations of Circulation Time to Cardiac Output and Circulating Blood Volume.—The velocity with which the blood flows is intimately related to the cardiac output and the circulating blood volume; all three circulatory variables are intimately correlated

with one another in the interests of the organism as a whole The quantitative interrelations between these three variables are, of course, very complex and influenced by many other factors But they may be expressed, in a general way, as follows:

Let V represent the *average* velocity of blood flow through a complete circuit; T the corresponding circulation time; M.V the minute volume of the heart (cardiac output); C.B.V the circulating blood volume; and C.S. the *average* cross-section of the vascular tree. Then,

$$M.V. = C.S. \times V$$

Since the circulation time is inversely proportional to the velocity of blood flow, this may be written:

$$M.V. = k \frac{C.S.}{T}$$

Inasmuch as the average cross-section of the vascular tree is determined by the filling, it is proportional to the circulating blood volume, *i.e.*.

$$C.S. = k_{I}\, C.B.V.$$

and

$$M.V. = k_{II} \frac{C.B.V.}{T},$$

an equation equivalent to the one long ago derived by Vierordt.[19]

Other factors being equal (which, of course, is probably never strictly true in the living organism with its multitudinous compensatory adjustments), the cardiac output is thus directly proportional to the circulating blood volume and inversely proportional to the circulation time. The circulating blood volume and the circulation time are adjusted to one another in the interests of maintenance of the cardiac output for which the metabolism of the moment calls This is beautifully illustrated in some cases of uncomplicated polycythemia vera. In these cases, the cardiac output is maintained at a normal level despite the elevated circulating blood volume by means of a corresponding increase in circulation time. On the other hand, in such conditions as fever, hyperthyroidism and exercise, in which a high cardiac output is called for, the increase in circulating blood volume is accompanied by diminution in circulation time.

As shown above, the quotient of circulating blood volume and circulation time affords a *relative* measure of the cardiac output, and has been used for the clinical estimation of the latter by Wollheim,[26] Seckel[15] and, in a modified form, Baumann[1] Wollheim terms this quotient the "circulation quotient." Using the dye method of determining blood volume and the fluorescin method for estimating the circulation time. Wollheim found that in normals the circulation quotient varies between 13 and 19, with an average of 16 2. He determined that the circulation quotient is increased in exercise, fever and Graves' disease, and decreased in circulatory failure. It is to be reiterated that, as yet, the determination of the circulation quotient does not substitute for the measurement of the cardiac output

For this to be the case, the value of the constant k_{II} will have to be known In fact, it seems improbable that k_{II} is more than a very rough "constant," especially in different individuals. Nevertheless, it would appear likely, although this also requires further study, that the determination of the circulation quotient affords a clinically useful, rough parallel to the cardiac output Wollheim points out that the method has the advantage that it involves only injections of dyes, and not the gasometric determinations required in the usual methods of estimating cardiac output, which require special facilities and training Moreover, the applicability of gasometric determinations of cardiac output in patients with pulmonary engorgement is often open to question

The Circulation Time in Circulatory Failure.—With the fluorescin method, Koch[12] showed that the arm-to-arm circulation time is prolonged in cardiac insufficiency. This was established on extensive material with the radium C method by Blumgart and Weiss, who made many important contributions in the field Of 100 patients with clinically evident heart failure studied by Tarr, Oppenheimer and Sager with the decholin method, with which the upper limit of normal is sixteen seconds, all had a circulation time of more than seventeen seconds, in 96, the circulation time was above twenty seconds, ranging up to forty-seven seconds

In quite extensive experience, I have seen few cases with either symptoms or signs of heart failure at rest in whom the circulation time by the saccharin method was not definitely prolonged However, it is not rare to encounter normal circulation time in individuals who are asymptomatic at rest but are dyspneic on exertion. Conceivably, future studies will show that such persons fail to accelerate the circulation on exercise as much as normals During improvement, dyspnea, edema and other manifestations of heart failure often lag behind the diminution in the circulation time The relatively fast circulation time in the failure of the thyrotoxic heart is discussed later (page 574). The circulation may also be fast in heart failure due to anemia or vitamin B deficiency, as well as in the presence of fever.

Compensated Cardiac Strain.—In the large majority of cases of well-compensated valvular disease or hypertension the circulation time is within normal limits (Koch, Blumgart and Weiss, Tarr, Oppenheimer and Sager). The same is true in angina pectoris and in auricular fibrillation and other arrhythmias without heart failure. Occasionally, one encounters slight prolongation of the circulation time in patients without flagrant symptoms of heart failure, but more careful examination usually reveals dyspnea on exertion and pulmonary engorgement in the roentgenogram In faultlessly compensated valvular lesions, the circulation time may be abbreviated by exercise quite as in health.

Failure of the Left Side of the Heart—The arm-to-tongue circulation time is prolonged in the vast majority of patients with isolated

failure of the left side of the heart. In 31 such patients studied by Hitzig, King and the writer[10] with the saccharin method, the circulation time was prolonged in 30. In severe cases, the circulation time may exceed forty-five seconds, *i. e.*, treble the normal. The prolongation of the arm-to-tongue circulation time in left heart failure is due almost entirely to retardation of blood flow through the pulmonary circuit. For the time which elapses in the arterial pathway from the left ventricle to the tongue can scarcely be prolonged enough to affect the total circulation time appreciably. And there is good evidence that blood flow from the antecubital vein to the right heart is not significantly, if at all, slowed. This is immediately indicated by the normal venous pressure in these cases. And with the radium C method, Blumgart and Weiss found that the arm-to-heart time is relatively fast Further, Hitzig, King and the writer[10] found that the circulation time from the antecubital vein to the arterial capillaries of the lung, measured with ether (page 52), is normal in some cases of left heart failure, which shows that there is no slowing of flow in the peripheral veins.

The finding of the last-named investigators that in some cases of left heart failure markedly prolonged saccharin time is accompanied by normal ether time (*e. g.*, thirty-five seconds saccharin time, six and a half seconds ether time in a patient with aortic and mitral valvular disease) shows that in these patients the slowing of blood flow is confined to the venous half of the pulmonary circuit, from the capillaries to the left side of the heart. Such findings are usually encountered at a relatively early stage of failure of the left side of the heart. The surplus blood in the pulmonary circuit resulting from the failure of the left heart is then accommodated entirely in the venous half of the circuit with resultant increase in the cross-section of the stream bed, the slowing of flow is an inevitable consequence of the increase in cross-section With more marked engorgement, the arterial half of the circuit is also implicated and the ether time is prolonged.

There is no strict parallelism between the prolongation of the circulation time and the intensity of the dyspnea and other symptoms of failure of the left side of the heart To a large extent, such discrepancies seem attributable to the absence of a constant relationship between the pressure in the pulmonary circuit and the velocity of blood flow through it Evidence cited in Chapter VII shows that hypertension in the lesser circulation is an important factor in the pathogenesis of dyspnea in left heart failure. When the right heart weakens, the pressure in the pulmonary circuit falls with relief of dyspnea and orthopnea But the arm-to-tongue circulation time is further prolonged by the addition of right-sided failure to the pre-existent left heart failure. The result is that in some such cases there is greatly prolonged circulation time with relatively little

dyspnea. I have repeatedly seen individuals, especially with hypertensive and arteriosclerotic heart disease, who were able to get about the ward despite a saccharin time of thirty-five seconds.

Contrariwise, there are also cases of isolated left heart failure in which, despite severe orthopnea and other evidences of intense pulmonary engorgement, the arm-to-tongue circulation time is but little prolonged, *e. g.*, to about twenty seconds Very rarely, the saccharin time in such individuals is within the limits of normal. In these cases, the right ventricle is sufficiently powerful to maintain the velocity of blood flow through the pulmonary circuit despite the increased resistance due to the left heart failure, though only at the expense of very high tension in the lesser circulation

Failure of the Right Ventricle.—Failure of the right ventricle prolongs both the arm-to-tongue (saccharin) and arm-to-lung (ether) circulation times This is seen most often when the right heart gives way subsequent to pre-existent left heart failure. In such cases, very long circulation times are not rare, *e g.*, saccharin time of over fifty seconds. Isolated failure of the right ventricle is far less common, but I have made observations of prolonged circulation time in right ventricular insufficiency secondary to emphysema and to fibroid phthisis.

Hypodiastolic Failure.—The arm-to-tongue circulation time may be greatly prolonged in the circulatory failure of mediastino-pericarditis and pericardial effusion.

Peripheral Circulatory Failure.—The circulation time in shock has been little studied. Wollheim[26] found but slight prolongation of the circulation time in the circulatory failure of the acute infections with decreased circulating blood volume, his cases evidently were suffering from what is termed peripheral circulatory failure in this book. The writer has several times found normal arm-to-tongue circulation time in post-operative shock. These observations indicate that in at least some form of shock the impairment of the circulation is due almost entirely to decrease in the circulating blood volume, and that the small quantity of blood in the vessels circulates at almost the usual speed. The matter needs further investigation.

Septal Defects.—An interesting aberration of the circulation time may occur in congenital defects of the interventricular septum with right-to-left shunt. In three such cases in children, McGuire and Goldman[13] observed with the cyanide method (page 51) that the arm-to-carotid sinus circulation time averaged four and two-tenth seconds, as contrasted with eleven and six-tenth seconds in the controls. Similar observations have been made by Dr. W. M. Hitzig. Obviously, the rapid circulation time is due to the cyanide avoiding the pulmonary circuit by making a short circuit through the patent septum. This can occur only when the septal defect is accompanied by right-to-left shunt. Presumably, a shortened

circulation time will also be observed when there is right-to-left shunt in interauricular septal defects or patent ductus arteriosus. In a patient with an acquired defect due to infarction of the interventricular septum, I found a slow circulation time; doubtless, there was no right-to-left shunt.

Recently, Dr. Puddu of Rome has written me of an interesting observation on patients with right-to-left shunt. A few seconds after he had injected ether to measure the arm-to-lung circulation time, the patient felt a violent shock in the head, this was evidently due to the ether passing directly into the arterial circulation and reaching the brain in considerable concentration.

Effect of Digitalis on Circulation Time.—Blumgart[4] and Weiss found that while digitalis has no effect on the velocity of blood flow in health, digitalization diminishes the circulation time in patients with heart failure. I have confirmed the latter finding on repeated occasions, in both isolated left heart failure (see Hitzig, King and Fishberg[10]) and in combined left and right failure, and in individuals with regular rhythm as well as those with auricular fibrillation. In one individual with auricular fibrillation, massive and successful digitalization reduced the saccharin time from thirty-six to fourteen seconds within twenty-four hours

Clinical Utility of Determination of the Circulation Time.—Knowledge of the circulation time is often of great aid to the clinician in the differential diagnosis of heart failure So simple a procedure as the determination of the circulation time is especially to be recommended to the general practitioner, for it requires neither laboratory facilities nor equipment other than a syringe, and can be carried out with ease in the home of the patient.

Theoretically, it seems probable that even were the determination of cardiac output suitable for clinical use on dyspneic patients, the circulation time would be a more delicate index of heart failure. Consider, for example, failure of the left side of the heart with pulmonary engorgement Under these circumstances, the volume of blood in the lungs is increased, which means that the cross-section of the pulmonary vascular bed is increased. In consequence of the greater cross-section the volume of blood traversing the pulmonary circuit per minute (the cardiac output) is not diminished proportionately as much as is the linear velocity of pulmonary blood flow Indeed, there is evidence that in exceptional instances the cardiac output is normal (page 42). And while I am not acquainted with comparative measurements of circulation time and cardiac output, it would seem that in at least most such instances with pulmonary engorgement, even though the cardiac output be normal, the pulmonary circulation time is retarded. Moreover, in severe cardiac failure in hypertension, the arm-to-tongue circulation time may be triple the normal despite the fact that the arterial pressure

is maintained at a high level. It appears very improbable that in these patients the cardiac output is correspondingly diminished, *i. e*, to one-third the normal. These considerations indicate strongly that heart failure affects the circulation time proportionately more than the cardiac output.

On the other hand, in shock with diminished circulating blood volume the reverse is probably true, *i e.*, the cardiac output is affected proportionately more than the circulation time. But more direct measurements are needed to prove this point

The diagnostic significance of the determination of the circulation time is due to the fact that it is prolonged in the vast majority of patients with symptoms due to heart failure It is of special value in the differential diagnosis of that very common condition, isolated left heart failure, from the following:

1. Bronchial asthma. The circulation time is prolonged in cardiac asthma, normal in bronchial asthma It should be remembered, however, that in elderly persons bronchial asthma and arteriosclerotic heart disease not uncommonly co-exist.

2. Dyspnea due to compression of the trachea or bronchi by aneurysm or mediastinal tumor, in which the circulation time is normal. Even in patients with syphilitic aortic insufficiency, I have several times established by finding normal circulation time that dyspnea was due to pressure on the bronchi by the dilated aorta and not to heart failure.

3. Dyspnea and cyanosis due to emphysema or other intrapulmonary or pleural conditions In emphysema without heart failure, the circulation time is normal (page 531). The same is true of pneumonia, while in unilateral complete pneumothorax the circulation time may be unusually fast, evidently because of the necessity for maintaining the minute volume of the right ventricle largely through one lung (observations by Hitzig, King and the writer).

Measurement of the circulation time is often also of aid in differentiating whether edema, enlargement of the liver or ascites are due to right heart failure or to primary renal or hepatic disease

The shortened circulation time in septal defect with right-to-left shunt (page 57) may be of diagnostic value.

The circulation time may also be of aid in following the progress of heart failure under treatment.

In evaluating the circulation time, it is important to bear in mind certain factors other than heart failure which affect it Myxedema and polycythemia are often accompanied by retardation of blood flow. On the other hand, thyrotoxicosis and to a much less extent fever and anemia may accelerate blood flow and thus tend to mask slight degrees of heart failure. These matters will be discussed in the special sections.

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CHAPTER IV

THE CIRCULATING BLOOD VOLUME

CHANGES in the circulating blood volume occupy a significant place among the mechanisms participating in the adaptation of the circulation to the metabolic demand, both in health and disease. Since ancient times, the conceptions of plethora and oligemia have been frequently invoked in the endeavor to comprehend the nature of various diseases. However, apart from such incidents as hemorrhage and transfusion, the blood volume was generally regarded as subject only to the rather slow changes resulting from the formation or destruction of blood. While this is largely true of the blood mass as a whole, the pioneer investigations of Barcroft[3] have revealed that the fraction of the total blood in the body which is in rapid circulation can change with remarkable rapidity, and that it is almost immediately adapted to various physiological demands, such as those imposed by exercise, emotion, pregnancy, low barometric pressure, and change in environmental temperature For example, a hot bath can increase the circulating blood volume in man up to 1300 cc. (Wollheim[47]). It would appear that increase in cardiac output, whatever the cause, is accompanied by synergistic augmentation in circulating blood volume. In disease also, as well as under the influence of various chemical agents, there may be quick and portentious alterations in the circulating blood volume Only in recent years, since the introduction of clinically applicable methods for measuring the circulating blood volume, has it been possible to study this important circulatory variable in disease; and though much has been learned, knowledge of the subject is as yet in its incipiency.

THE CIRCULATING BLOOD AND THE BLOOD DEPOTS

In an expedition to the tropics, Barcroft made the momentous observation that the blood volume as measured by the carbon monoxide method (page 68) increased in the warmer climate over what it had been in the temperate zone, and that with return to cooler regions the blood volume dropped to its previous level. Experiments on man and various animals showed that such a rise in blood volume could be induced very rapidly by increase in environmental temperature, exercise or emotion. These observations made it clear to Barcroft that the body possesses depots of blood which can be mobilized into the general circulation very rapidly by the appropriate stimulus.

The total volume of blood in the body thus consists of two components:

1. The blood which is in rapid general circulation, the so-called circulating blood volume.

2. The depot or reserve blood, situated in organs to which, from this point of view, the term blood depot is applied. "To be a blood depot an organ must clearly contain important quantities of blood which are unnecessary or at least temporarily unnecessary for its own metabolism and which can be transferred to other organs in order to meet their needs" (Barcroft, Benatt, Greeson and Nisimaru[5]). The enormous utility to the organism of having such reserve supplies of blood available for emergencies—as when blood is lost by hemorrhage or when extraordinary quantities of blood are required by the muscles in exercise—is obvious

Three varieties of blood depots may be recognized:

1. Blood depots in the narrower sense, in which blood is almost completely side-tracked from the circulation, exemplified by the spleen.

2. Blood depots composed of extensive capillary and venous networks, as in the skin.

3. Blood depots functioning by means of a venous throttle mechanism, as the liver.

The Blood Depots in the Narrower Sense—The Spleen.—In the most restricted sense of the term, a blood depot is an organ in which blood is stored in diverticulæ from the general stream bed so as to be almost completely side-tracked, these diverticulæ being emptied into the general circulation in response to the adequate stimulus

Barcroft and his pupils have shown that in the dog, rat, rabbit and other animals, the spleen constitutes a blood depot of this type. They demonstrated the almost complete side-tracking of blood in the spleen from the general circulation by allowing the animals to inhale carbon monoxide When the animal was at rest, there was a long lag between the time when the blood in the general circulation attained a certain concentration of carbon monoxide hemoglobin and when this concentration was reached by the blood in the spleen In the experiments of Hanak and Harkavy[25] on guinea-pigs, up to six hours elapsed before the hemoglobin of the blood in the splenic pulp had taken up as much carbon monoxide as the streaming blood. On the other hand, when guinea-pigs were made to kick about, such equilibrium was attained within two minutes, showing that during exercise the blood in the spleen is no longer side-tracked and participates vivaciously in the general circulation. In further experiments, Barcroft and Stephens gave a direct demonstration of the mobilization of blood from the spleen of the dog by showing that the organ contracts to one-half or one-third of its previous size during severe exercise. The same occurred when the circulating blood volume was

depleted by hemorrhage or when the environmental temperature was elevated. Barcroft further demonstrated that the mobilization of blood from the spleen is regulated through the central nervous system.

The quantitative significance of the spleen as a blood depot probably varies in different species In dogs, Barcroft and Stephens[8] estimate the amount of blood that can be mobilized from the spleen as forming one-fifth of the total volume in circulation. Cruickshank[16] and Barcroft and Poole[7] found that the blood of the splenic pulp which is mobilized from the organ may contain a considerably higher concentration of red corpuscles than the general circulation. The contribution of the splenic blood to the oxygen-carrying capacity of the circulation is thus greater than that indicated by the decrease in size of the spleen when it contracts

That the human spleen serves as a blood depot seems highly probable from the close morphological resemblance of its pulp to that of the animals in which mobilization of blood from the spleen has been experimentally demonstrated The size of the spleen in man indicates that its rôle as a depot is not quantitatively as notable as in some of the smaller mammals However, the dimensions of the spleen during life are considerably greater than the post mortem appearance of the organ suggests. And when the spleen is enlarged, it can store very considerable quantities of blood Following the injection of epinephrin, I have seen diminution in the size of the enlarged spleen sufficient to indicate that at least a liter of blood had been mobilized into the circulation

Some data for the quantitative evaluation of the depot function of the human spleen have been presented by Dresel and Beitner[17] They found that the ingestion of large volumes of fluid is ordinarily followed by increase in both the circulating plasma and the circulating red cell volume, the latter amounting to about 12 per cent. It appeared that the increase in red cell volume was due to mobilization from the spleen, for in 7 individuals who had undergone splenectomy equal fluid ingestion resulted in increase of only the circulating plasma volume and not that of the red cells. Unfortunately, they actually determined only the circulating plasma volume and calculated from the hematocrit reading the corpuscular volume, that this calculation is not unobjectionable will be seen on page 68.

But the significance of even moderate increase in circulating blood volume, such as may come from the human spleen is not to be underestimated, for, as Barcroft points out, experiments on the heart-lung preparation indicate that the addition of comparatively small quantities of blood to the circulation induces disproportionately great increments in cardiac output.

The capsule of the human spleen, contrary to that of many other mammals, contains very little smooth muscle. Contraction of the

capsule is therefore probably not important in squeezing blood from the human spleen, as is doubtless the case in the dog and other species. Vasomotor mechanisms evidently predominate in mobilizing blood from the human organ.

Whether or not there are other blood depots of the same type as the spleen remains to be demonstrated. The histological structure indicates that this may be true of the bone marrow and of the hemolymph nodes when they are present

Blood Depots Composed of Capillary and Venous Networks—The Skin.—A second variety of blood depots is exemplified by the skin This was demonstrated by Meek and Eyster.[34] They found that a short time after transfusion into dogs the injected blood had been removed from the active circulation. Photomicrographs of the capillaries and venules of the skin of the ear showed that these vessels were acting as reservoirs. Another observation illustrating the storage of blood in the capillaries of the skin was made by Abel, Geiling and Kolls.[1] They found that following the injection of histamine or albumoses into the dog the skin capillaries were dilated. That this blood was actually removed from the active circulation was shown by the simultaneous decrease in the size of both sides of the heart

The rôle of the skin as a blood depot in man has been studied in detail by Wollheim [47] He finds that the subpapillary capillary and venous plexuses of the skin form a very capacious blood depot, especially when these vessels are dilated, as is the case in cyanotic skin. According to Wollheim's observations with the capillary microscope, the rate of blood flow in the subpapillary capillary network is from five to twenty times slower than in the adjacent end capillaries of the skin papillæ He showed that widening of the subpapillary plexuses is accompanied by diminution in the circulating blood volume, the blood removed from the active circulation evidently being largely stored in these plexuses. Wollheim found that the circulating blood volume as determined by the dye method diminishes between 400 and 1800 cc. when the subject sits with the legs hanging down. In his opinion, the blood removed from the active circulation is stored in the subpapillary plexuses of the skin of the dependent lower extremities.

Further evidence that cyanosed human skin serves as a blood depot has been adduced by Barcroft, Benatt, Greeson and Nisimaru.[5] They flushed one hand by immersion in warm water and cyanosed the other in cold water. The subject then inhaled carbon monoxide. Barcroft and his associates found that the rise in carbon monoxide content of the cyanosed hand was slower, the maximum concentration was lower and attained later, and the subsequent elimination of the gas was retarded in the cyanosed hand. These

experiments show that at least some of the red corpuscles are retarded in their flow though cyanosed skin.

The subpapillary plexuses seem to be primarily a depot for the corpuscles. A number of observers have found that in health the blood from the skin contains the same concentration of erythrocytes as that from a large vein. On the other hand, the red cell count in the blood of the minute vessels of the skin is increased when these vessels are dilated and gorged with blood. Thus, Cannon, Fraser and Hooper[14] found that the cutaneous blood of individuals in shock has a much higher red cell count than the general venous blood. Wollheim[47] also observed that blood obtained from cyanosed skin contains between 800,000 and 1,000,000 more erythrocytes per cubic millimeter than does the circulating blood It is true that this concentration of red cells in the dilated subpapillary plexuses may be purely a secondary phenomenon attributable to increased transudation from the dilated capillaries. Nevertheless, the result is storage of predominantly cellular elements in the minute vessels of the skin, a fact which is of great importance in the interpretation of blood volume determinations (page 69)

It is to be emphasized that the subpapillary capillary and venous plexuses constitute blood depots in only a *relative* sense There is no almost complete side-tracking of blood from the circulation as in the pulp of the spleen But because of the large capacity and network-like arrangement of the capillaries and venules of the skin, the flow is very slow when these vessels are dilated For this reason, they may hold a large volume of blood and discharge extremely little of it per minute into the general circulation The consequence is that the contribution of the blood in these vessels to the venous return to the heart, and therefore to the cardiac output, is very small On the other hand, when any stimulus contracts the vessels of the subpapillary vessels, a large amount of blood is returned to the heart and the cardiac output is correspondingly increased

The studies of Jarisch and Ludwig[28] indicate that the capacious capillary networks of the *intestinal wall* function as a blood depot in a manner analogous to the cutaneous subpapillary plexuses.

Blood Depots Functioning by Virtue of Venous Throttle Mechanisms—The Liver.—A third type of blood depot is that regulated by a venous throttle mechanism, *i. e.*, in which the efferent veins are especially adapted to powerful constriction which imprisons blood in the organ, and releases it into the general circulation when the constriction is relaxed

The most important depot of this variety is the liver. Krogh[30] long ago pointed out that the liver, by virtue of its ability to hold large quantities of blood, is a most important regulator of the venous return to the right heart and therefore of the cardiac output. The

small portal tributaries serve as a primary resistance and the hepatic veins as a secondary resistance, by the coördinated adjustment of these two resistances, the amount of blood in the liver can be varied within wide limits.

Subsequent studies by Lamson and Roca,[31] and in great detail by Mautner and Pick[33] showed that a most important regulator of the blood content of the liver, at least in certain species, is the tone of the large hepatic veins. Mautner and Pick found that the injection of histamine or peptone into the dog is followed by constriction of the hepatic veins with damming back of large volumes of blood into the liver. Their conception is that at least a large part of the reduction in circulating blood volume in the shock produced by these substances is a result of the storage of blood in the liver. Mautner and Pick believe that in consequence of the increased tension in the hepatic capillaries due to the venous block, transudation of large volume of plasma into the liver takes place, thereby accounting, at least in part, for the concentration of the corpuscular elements of the blood in these forms of shock. The constriction of the hepatic veins of the dog in peptone shock, with resultant filling of the liver with blood, has been confirmed by Simonds and Brandes.[44] Bauer, Dale[9] and their co-workers have shown that the action of epinephrin on the hepatic veins of the dog is diametrically opposed to that of histamine; they find that epinephrin relaxes the hepatic veins with resultant discharge of blood from the liver into the general circulation. Although the existence of a throttle mechanism in the hepatic veins of the dog has been disputed by Schretzenmayr,[42] it seems to have been definitely established by the above-mentioned experiments. Moreover, Simonds and Arey[43] have found that the hepatic veins of the dog contains an exceptionally large amount of smooth muscle, which doubtless is correlated with their sphincteric action. Popper[39] showed that in the dog constriction of the hepatic veins may result in complete closure of the lumen.

In the functioning of the hepatic blood depot, the throttle action of the hepatic veins is integrated with synergistic changes in the small vessels of the liver. Thus, there is evidence that the constriction of the hepatic veins by histamine is accompanied by dilatation of the minute vessels in the liver, and the relaxation of the hepatic veins by epinephrin is coordinated with constriction of the small intrahepatic radicals In the case of histamine, both mechanisms act to retain blood in the liver and thus diminish the venous return to the heart, while with epinephrin the reactions of both the hepatic veins and the small vessels cooperate to drive blood out of the liver and increase the venous return to the heart

In man, the hepatic veins contain only a small amount of smooth muscle, far less than in the dog (Popper[39]). This would indicate

that the throttle mechanism is much less significant in man than in the dog, and that the human liver functions as a depot more through alterations in the caliber of the small vessels as described by Krogh (page 65) than through the venous throttle mechanism. That the liver serves as a blood depot through increase in the capacity of its vessels, and not by side-tracking the blood into diverticulæ from the main current as does the spleen, is indicated by the work of Barcroft, Nisimaru and Ray.[6] They find that following the inhalation of carbon monoxide, there is no delay in the taking up of the gas by the blood in the liver, as is the case in the spleen (page 62). The hepatic blood depot is very significant for the circulation as a whole because of its great capacity This has been studied by Grab, Janssen and Rein[22] with the Thermostromuhr. They find that in the dog from 50 to 75 per cent of the blood flow in the inferior vena cava comes from the liver. They estimate the amount of blood stored in the liver depot by emptying it with an injection of epinephrin This method indicates that the volume of blood stored in the liver is from 26 to 59 per cent of the weight of the organ after the action of epinephrin, which is more than the quantity of blood deposited in the spleen.

In addition to its function as a depot for erythrocytes, which are held within the capillaries, it seems likely that the liver can also store plasma within the hepatic cells, thus acting as what Ludwig[32] calls a "plasma depot" Ludwig has advanced experimental evidence that the liver cells in the dog can store large quantities of blood plasma, for example, during shock. Performing angiostomy on the portal and hepatic veins, he found that the liver cells can remove fluid from the blood circulating through the organ and under appropriate conditions return it again to the circulating medium

METHODS FOR DETERMINING THE CIRCULATING BLOOD VOLUME AND NORMAL VALUES

The technic of estimating the circulating blood volume will not be described here; an excellent discussion is given by Peters and Van Slyke.[37] It may be mentioned, however, that two methods are in general use for the determination of the circulating blood volume·

1. The determination of the circulating *plasma volume* by the injection of a dye (Keith, Rowntree and Geraghty[29]). A known amount of a colloidal dye (vital red, Congo red, Evans blue, etc.) is injected intravenously. After the lapse of sufficient time for thorough admixture, the concentration of the dye in a blood specimen is determined. An accurate technic for clinical use has been developed by Gibson and Evans[20] who inject Evans blue and deter-

mine the concentration of the dye with the spectrophotometer. Since the dye is suspended in the plasma, the circulating plasma volume can be calculated from this concentration and the amount injected. The circulating blood volume is calculated from the circulating plasma volume and the hematocrit reading. Brown and Rowntree[13] find with the dye method that the circulating blood volume of normal persons is between 70 and 100 cc. per kilogram of body weight in 98 per cent, and the circulating plasma volume between 40 and 60 cc. per kilogram in 96 per cent, of the subjects tested Brown and Keith[12] have shown that the circulating blood volume is relatively low in comparison with the weight in the obese and relatively high in the thin. They are of the opinion that the blood volume is more intimately correlated with the body surface than with the weight. With vital red, Brown and Keith find the normal circulating plasma volume between 1400 and 2500 cc. and the circulating blood volume between 2500 and 4000 cc. per square meter body surface. Brown and Rowntree state that simultaneous determinations of the circulating blood volume by the dye method with blood from both arms do not differ by more than 2 per cent, while Wollheim[47] estimates the error of the method as about 5 per cent

2. The determination of the circulating *erythrocyte volume* by the inhalation of carbon monoxide (Haldane and Smith[23]). Since carbon monoxide combines with hemoglobin, knowledge of the concentration of carbon monoxide in a specimen of blood and of the amount of the gas absorbed enables the calculation of the circulating erythrocyte volume. From the hematocrit reading, the circulating blood volume is calculated. In healthy young adults, Chang and Harrop[15] find with the carbon monoxide method that the circulating blood volume is between 63 and 76 cc per kilogram of body weight, other investigators give similar figures. The carbon monoxide method thus yields lower values for the circulating blood volume *in health* than does the dye method In circulatory failure, the reverse may be true. Among the reasons for these differences are the following:

With both methods, the calculation of the circulating blood volume from the hematocrit reading in the blood of the antecubital vein involves the assumption that the ratio of erythrocytes to plasma *is the same throughout the circulating blood. Whether this assumption* is justifiable is questionable, especially in circulatory failure. It is true that Hitzenberger and Tuchfeld[27] found that in individuals with various pathological conditions the cell-plasma ratio was the same in blood from a large artery, a large vein, and the skin of the finger tip and lobe of the ear. They also found the same true of blood from various visceral vessels in the dog. But they did not study the visceral vessels in circulatory failure in man. On the

other hand, Smith, Arnold and Whipple[46] believe there is sufficient evidence to indicate an excess of plasma over red cells in arterioles and capillaries. In fact, Midsuno (quoted by Ewig) found that normally many capillaries contain only plasma. Since the carbon monoxide method measures the red cell volume and the dye method the plasma volume, it is easy to see on this basis why, with hematocrit readings in blood from a large vein, the calculated circulating blood volume by the former is the smaller. Smith, Arnold and Whipple therefore believe that in order to obtain accurate blood volume determinations, it is necessary to determine the red cell volume by the carbon monoxide method, the plasma volume with the dye method, and add the two (with the addition of about 0 2 cc per 100 grams of body weight for the leukocytes). For clinical purposes, however, the dye method suffices. Because of the relative ease with which it is carried out, the dye method is used almost exclusively in hospitals in this country, the carbon monoxide method being applied only in investigations.

Ewig[18] has found that in heart failure, contrary to health, the carbon monoxide method gives a higher blood volume reading than does the dye method He explains this on the basis of Aschoff's finding that in passively congested organs many capillaries are packed tight with erythrocytes with but little surrounding plasma.

It will be noted that the above discussion is confined entirely to the *circulating* blood volume As yet, no method is available for determining in man the *total* blood volume—the circulating blood plus the depot blood—although Baumann[10] made an attempt in this direction. Some conception of how considerable is the volume of the depot blood may be derived from the observations of Ewig and Hinsberg.[19] They found that by such means as exercise or an electric light bath of one hour's duration, they were able to increase the circulating blood volume as much as 15.7 per cent This figure represents blood mobilized from the depots, and it is highly improbable that all the blood stored in the depots has been brought into the circulation by the means employed In the resting dog, Barcroft[3] estimates that about 46 per cent of the total blood volume is stored in the depots, and the percentage in man may well approach this.

THE BLOOD VOLUME IN CIRCULATORY FAILURE

Various influences come to bear upon the blood volume in the different types of circulatory failure. Both the plasma and the cell volume may be affected, together or independently In an individual case, the net result is doubtless a summation of several factors. Among the mechanisms through which circulatory failure affects the blood volume are the following:

1. Heart failure is almost invariably accompanied by dilatation of one or more of the cardiac chambers. Often, this dilatation amounts to 500 cc. or more; indeed, there are cases of mitral stenosis in which the left auricle alone holds a liter. This increase in the blood content of the cardiac chambers entails—in order that the rest of the vascular bed be adequately filled—corresponding augmentation in total circulating blood volume

2. The segment of the circulation upstream to a failing chamber—the pulmonary circuit in left heart failure and the systemic veins in right heart failure—is the seat of passive engorgement. How large a volume of blood may be concerned in such engorgement is illustrated by the finding of Hamilton[24] and his associates that the normal intrathoracic blood content of about 2 liters may be increased to 4 liters in patients with heart failure. Engorgement of one portion of the circulation must obviously be accompanied by corresponding increase in total circulating blood volume if the remainder of the vascular bed is not to be depleted.

3. The example of the polycythemia of high altitude shows that oxygen want stimulates the formation of red cells. It is to be presumed that this mechanism operates to increase the circulating red cell volume in heart disease with arterial anoxemia In some cases of congenital cyanosis the circulating red cell volume is prodigious.

4. The formation of edema tends to decrease the plasma volume, the resorption of edema the reverse. Peters, Bulger, Eisenmann and Lee[36] find that protracted occlusion of the venous return from the arm may cause 30 per cent concentration of the plasma as a result of loss of fluid to the tissues.

5. The oliguria of circulatory failure, insofar as it is of renal origin, tends to increase the plasma volume, while the opposite is true of polyuria during improvement.

6. The decrease in colloid osmotic pressure of the plasma so common in heart failure (page 197), as well as the various changes in the crystalloids of the blood, influence the fluid exchange between blood and tissues This factor doubtless affects not only the volume of the plasma but also the size and therefore the total volume of the erythrocytes, although the latter change may be small.

7. It remains to be determined whether circulatory failure deranges the mechanism regulating the mobilization of blood from the depots into the circulating blood, and *vice versa*. Wollheim[47] and Ewig and Hinsberg[19] observed that while in health such procedures as exercise and electric light baths increase the circulating blood volume through mobilization from the depots, in heart failure these measures are not followed by such an effect. Possibly, this phenomenon is due to previous emptying of the blood depots into

the general circulation as a result of the heart failure through the first three mechanisms mentioned above.

8. In peripheral circulatory failure (shock) various mechanisms operate to diminish either the circulating plasma or whole blood volume; they are discussed in Chapter XXXI.

9. Therapeutic measures may influence the circulating blood volume. Thus, Wollheim[47] found that injection of 2 cc. of digipuratum decreases the circulating blood volume between 300 and 1600 cc. Mies[35] and Ewig and Hinsberg[19] also observed that injection of strophanthin decreases the circulating blood volume, the effect lasting from twenty-four to thirty-six hours. Wollheim found that caffein increases and morphine decreases the circulating blood volume, though not constantly In his experiments, subcutaneous injection of 1 mg. of histamine decreased the circulating blood volume between 300 and 1400 cc. in four to twenty minutes Epinephrin increases the circulating blood volume These alterations in circulating blood volume occur so rapidly that they must be due to displacements of blood between the depots and the active circulation This is sometimes easily seen when epinephrin is injected into a patient with splenomegaly; the spleen may quickly diminish in size. In the rabbit, Mies[35] found that the decrease in circulating blood volume produced by strophanthin is accompanied by a rise in the weight of the liver and spleen.

Fluid or salt restriction or ingestion may affect the circulating blood volume.

As a result of the interaction of these different factors, the blood volume in circulatory failure may deviate considerably from the normal, and in either direction. The most important determinant of the circulating blood volume seems to be the type of circulatory failure present, whether cardiac or peripheral. In the peripheral circulatory failure of shock, as will be discussed in detail in Chapter XXXI, the circulating blood volume is decreased. In heart failure, on the other hand, recent investigations have shown that the characteristic and most common change is increase in circulating blood volume.

The Circulating Blood Volume in Heart Failure.—It has long been known that at the necropsy of an individual who has succumbed to protracted heart failure, one generally finds an unusually large amount of blood in the different viscera and in the heart and great vessels. This general impression of increased volume of blood in the cadavers of cardiac patients has been confirmed by the systematic observations of Aschoff,[2] who found much more blood in the heart and vessels of such bodies than in cases in which the heart had not been insufficient.

Some of the early investigators using the dye method of determining the circulating blood volume obtained normal values in

heart failure (Keith, Rowntree and Geraghty,[29] Bock[11]). However, Plesch[38] showed subsequently with the carbon monoxide method that the circulating blood volume is generally elevated in cardiac failure and falls as the heart improves. Using the dye method, Rowntree and Brown[41] found the circulating blood volume high in cardiac edema with proportionate increase in cells and plasma. In very extensive investigations with the dye procedure, Wollheim[47] found the blood volume elevated in most instances of circulatory failure but low in others; his observations are discussed further below. Wollheim[47] showed that in the same patient the circulating blood volume may be from 600 to 2800 cc. greater when decompensated than when compensated, the difference generally being between 1000 and 1600 cc. While 100 of Wollheim's compensated patients had an average circulating blood volume of 70 cc. per kilogram of body weight, 100 decompensated individuals had, despite the edema, an average of 84 cc. Heilmeyer and Riemenschneider[26] observed an average circulating blood volume (dye method) of 8.5 per cent of body weight in decompensated heart disease, as contrasted with 7.7 per cent in normal controls. Hitzenberger and Tuchfeld[27] (carbon monoxide method) found increased circulating blood volume in decompensated valvular disease and emphysema but not in hypertension and coronary sclerosis. With the carbon monoxide method, as well as with a combined dye and carbon monoxide procedure which constitutes the most reliable method (page 67), Ewig and Hinsberg[19] found increased circulating blood volume in all varieties of heart failure. They also observed diminution in circulating blood volume with the restoration of compensation, especially when this was accomplished with the aid of digitalis. Uhlenbruck and Vogels[46] observed diminished circulating blood volume (dye method) in cases of heart failure accompanied by marked edema In other instances of heart failure—both right- and left-sided—they noted elevated circulating blood volume.

What is probably the most accurate available data on the blood volume in heart failure has been obtained by Gibson and Evans.[21] Their findings show clearly that development of chronic heart failure is accompanied by progressive increase in the volume of plasma and red cells. The augmentation of plasma volume is proportionately a little less than that of the corpuscles. Gibson and Evans find that the blood volume mounts roughly in proportion to the elevation of venous pressure and the slowing of circulation time. In severely decompensated patients they find that the circulating blood volume averages more than 50 per cent above normal. With restoration of compensation, the blood volume declines.

Summarizing these findings, it has been demonstrated, as stated above, that *heart failure is characteristically accompanied by increase in circulating blood volume.* The latter is due largely to the increment

in the volume of blood contained in the dilated heart and in the engorged parts of the circulation upstream to the failing chamber or chambers Other factors mentioned above may also be concerned. However, it appears that in some cases the tendency to increase in circulating blood volume as a result of heart failure is counteracted by loss of plasma water in the formation of massive edema, or by complication with the peripheral circulatory failure of shock. It should be remembered (page 69) that in heart failure the dye method may reveal too low a circulating blood volume because of the presence in passively engorged organs of capillaries packed tight with red cells and containing little plasma. On a number of occasions, necropsy on individuals succumbing to heart failure has revealed such large quantities of blood in the lungs, heart, liver, and splanchnic area that the moderate increase in circulating blood volume determined during life by the dye method has seemed to me a decided underestimate.

Briefly, it may be said that chronic heart failure is characterized by an increased blood volume and most forms of peripheral circulatory failure by decreased blood volume. But there is this difference: In the former instance the increased blood volume is a *consequence* of the heart failure, while in the latter case the decreased volume is the *cause* of the circulatory failure.

CIRCULATING BLOOD VOLUME IN COMPENSATED HEART DISEASE

In compensated cardiac lesions, Wollheim finds the circulating blood volume below normal. On the other hand, the studies of Ewig and Hinsberg[19] indicate no constant change; they find normal, high and low circulating blood volume in compensated cardiac strain. Gibson and Evans find the blood volume of the compensated cardiac to vary little from the normal. But whatever the absolute value of the circulating blood volume, the investigations quoted above show that as the insufficient heart compensates, the circulating blood volume decreases This seems to be especially true when digitalis has been administered

Wollheim's Plus and Minus Decompensation.—In a detailed series of investigations, Wollheim[47] has differentiated two varieties of circulatory decompensation on the basis of the circulating blood volume, namely *plus decompensation*, in which the circulating blood volume is above normal, and *minus decompensation*, in which it is subnormal. Plus decompensation is much more common than the other *In plus decompensation, the circulating* blood volume falls with restoration of compensation, while in minus decompensation it rises as the patient improves Both varieties occur in the same basic conditions, such as valvular disease, hypertension and emphysema But the cause of the break in compensation is different. Wollheim finds that plus decompensation most often results from overexertion or the onset of auricular fibrillation, while minus decompensation is generally, though not always, due to infection. He also gives diagnostic

criteria for clinical differentiation of the two types of decompensation. In plus decompensation, Wollheim states that dyspnea is less when sitting up with hanging legs, cyanosis is slight and only acrocyanosis, the patient is wakeful, and the cervical veins are well filled In minus decompensation, on the contrary, dyspnea is less when reclining, though there may be orthopnea, cyanosis is widespread over the surface of the body, the patient is tired and often somnolent, and the cervical veins are but poorly filled

Wollheim attributes minus decompensation to toxic destruction of protein in fever with resultant liberation of histamine-like substances which cause relaxation of the capillaries in the depots and consequent withdrawal of blood from the rapid circulation into the depots The venous return to the heart is thus reduced and with it the cardiac output, the heart muscle, like other tissues, suffers from inadequate blood supply. Wollheim believes that plus decompensation is also precipitated by disturbance in the function of the blood depots But here the trouble is that the blood depots discharge so much blood into the active circulation that the damaged heart is unable to master it The cause of this disturbed function of the blood depots is not clear

Wollheim's investigations are very interesting and he has adduced much important data on the blood volume in circulatory failure. However, most other investigators (*e g.*, Romberg,[10] Ewig and Hinsberg,[19] Uhlenbruck and Vogels[16]) do not agree with his interpretation of the findings It seems highly probable, as stated above, that increase in circulating blood volume indicates that circulatory failure is due to *cardiac* insufficiency, while a low circulating blood volume occurs characteristically in circulatory failure of *peripheral* origin Wollheim's cases of protracted minus decompensation would seem to be instances of protracted peripheral circulatory failure—a state that can be present for weeks—although he does not admit the identity. It is to be borne in mind that peripheral circulatory failure with resultant shock may appear in patients with cardiac disease, notably as a result of infection This, however, is to be differentiated sharply from progress of the cardiac insufficiency The careful studies of Gibson and Evans[20,21] never revealed an increase in blood volume during recovery from true cardiac failure; they regard "minus decompensation" as a misconception due to technical inadequacies

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CHAPTER V

THE ARTERIAL PRESSURE AND PULSE, ALTERNATION OF THE PULSE

It might be anticipated that circulatory failure, so often accompanied by diminution in cardiac output, would be invariably manifested by fall in arterial pressure While more or less depression of the arterial tension is frequently occasioned by circulatory insufficiency, this is by no means always the case, especially when the latter is due to cardiac weakness In many instances of heart failure, there is comparatively little change in either the systolic or the diastolic pressure. It is commonplace to observe patients who suffer from such manifestations of heart failure as dyspnea, cyanosis, edema, and swelling of the liver, despite the fact that the arterial pressure is maintained at its previous level. Indeed, there are instances in which heart failure is accompanied by rise in blood pressure, which again falls as the heart improves And in arterial hypertension the blood pressure remains elevated despite the supervention of severe heart failure.

On the other hand, the arterial pressure is almost always depressed in circulatory failure of peripheral origin (shock), often to an extreme degree. But even in the case of peripheral circulatory failure, there are circumstances in which the arterial pressure is maintained or elevated for a considerable time (page 621).

REGULATION OF THE ARTERIAL PRESSURE IN HEART FAILURE

The fact that the arterial pressure is so often maintained in heart failure is really not surprising. Of course, in those instances in which the failing heart holds up its output per minute by tachycardia and other compensatory mechanisms, one would not expect a drop in arterial pressure. And even when there is a considerable drop in the minute volume of the heart, as long as the vasomotor regulations function efficiently, the blood pressure can generally be maintained at its previous level. This is readily understood from the following consideration of the laws governing the flow of fluids in narrow tubes, previously discussed in another, related connection. These laws, first studied by Poisseuille and named after him, are embodied in the formula,

$$P = \frac{8nLQ}{\pi R^4}$$

where,
P is the pressure
n, the coefficient of viscosity
L, the length of the tube
Q, the volume of flow per unit of time (minute volume)
R, the radius of the tube.

From this equation, it is seen that while the pressure varies with the first power of the viscosity and the minute volume, it varies inversely with the *fourth* power of the radius of the tube. In other words, doubling the output of the heart or the viscosity of the blood will only double the blood pressure, but halving the radius of the small vessel will increase the pressure sixteen times. While the laws of Poisseuille do not hold exactly for the branching circulation, it seems clear from the studies of Hess,[10] Tigerstedt,[37] and others that they furnish valuable approximations which are at least of the correct order

These results indicated that the blood pressure is more readily influenced by changes in the caliber of the arterioles than by variations in the output of the heart or in the viscosity of the blood. As Tigerstedt puts it, "The blood pressure, though dependent in equal degree on the resistance and the minute volume, is controlled above all by the momentary degree of contraction of the vessels. If the vessels are strongly dilated, the heart cannot contain and expel a volume of blood sufficiently great to maintain the blood pressure at a high level. On the other hand, one may say that there is no limit to the increase in resistance, for by sufficiently strong stimulation of the vasomotor nerves the lumen may be obliterated, and at a great resistance a small volume of blood suffices to keep the blood pressure at a high level"

It is thus clear that by a comparatively small degree of peripheral vasoconstriction the arterial pressure will be maintained even though cardiac weakness results in considerable decrease in the minute volume of the heart. There is every reason to believe that such regulatory vasoconstriction is actually the most important means of keeping up the arterial pressure despite a failing heart. This vasoconstriction may well be advantageous from another point of view. For with progressive diminution in the output of the heart there is increasing danger of inadequate blood supply to such vital organs as the heart and the brain. A higher degree of vasoconstriction in the splanchnic area, the skin, and the muscles would not only serve to maintain the blood pressure, but would result in a larger fraction of the minute volume being distributed to the brain and the heart. Such conception is in good accord with the frequent observation of cold extremities in, for example, patients with tight mitral stenosis who are well enough to be up and about, have no evidences of deficient blood supply to the brain, and in whom, if middle aged or elderly, the blood pressure is not uncommonly ele-

vated. It is to be presumed that this vasoconstriction is a manifestation of the complex regulatory mechanism which, in health as well as in disease, functions to prevent untoward fluctuations of blood pressure. So far as I know, the details of how this mechanism functions in heart failure have not been investigated, conceivably, a drop in arterial pressure due to diminished cardiac output reflexly stimulates the vasomotor center through the carotid sinus and aortic nerves with resultant vasoconstriction and restoration of the previous blood pressure. But this is merely a hypothesis.

Accessory Factors Affecting the Arterial Pressure in Heart Failure.—In the foregoing, it has been seen that the two primary factors influencing the blood pressure in heart failure are decrease in cardiac output, which tends to lower it, and peripheral vasoconstriction, which tends to elevate the arterial tension

In addition to these, a number of other factors may come into play in individual instances.

Abbreviation of Diastole—The tachycardia that is so often present in circulatory failure shortens diastole As a result, there is less time for the blood to flow out of the arteries before the next systole and the diastolic pressure does not fall as low as it would with a slower heart rate This may well be a factor of some significance in the production of the relatively high diastolic pressure (and consequently small pulse pressure) that is sometimes present in heart failure. The converse of the phenomenon is seen in heart block, in which the long diastole results in preternatural emptying of the arteries and consequent low diastolic pressure

Changes in the Composition of the Blood.—It has been suggested that changes in the chemical composition of the blood resulting from heart failure stimulate the vasomotor centers with consequent vasoconstriction and tendency to elevation in blood pressure. The changes considered have been decreased oxygen content and accumulation of carbon dioxide; acidosis due to increase in lactic and other fixed acids also comes into question. That these changes in the blood gases stimulate the vasomotor center is generally accepted (see, however, page 79) But it will be seen in Chapter VII that there is neither arterial anoxemia nor carbon dioxide retention in the large majority of instances of heart failure, only when pulmonary changes become very pronounced do these changes in the blood gases appear. Evidently, then, the pressor effects of anoxemia or carbon dioxide retention come into question only in the cases of heart failure with extensive pulmonary changes And any considerable accumulation of lactic acid occurs only in extreme cardiac failure (page 133)

The high degree of anoxemia or carbon dioxide retention necessary, *per se*, to elevate the blood pressure appreciably is indicated by the experimental observations of Cobet.[2] He found that the vasomotor

centers are not nearly as sensitive to these stimuli as are the respiratory centers. Thus, while inhalation of carbon dioxide sufficient to lower the pH of the blood 0 15 produced dyspnea that was hardly bearable, the arterial pressure rose only about 20 mm. of mercury. And he also found that with intact circulation, the oxygen content of the blood had to be decreased at least 25 per cent to elevate the blood pressure 30 mm

However, it is to be presumed that when heart failure is accompanied by cerebral arteriosclerosis or results in pronounced slowing of blood flow, smaller changes in the blood gases will suffice to exert pressor effects For the increase in the acidity of the centers due to the slowing of blood flow will be summated with the changes in the chemical composition of the blood

The most striking elevation of blood pressure due to cardiac failure, one which apparently results primarily from anoxemia and perhaps also carbon dioxide retention, is that frequently observed in the acute pulmonary edema of left ventricular failure In these patients, asphyxia follows the filling of the alveoli and bronchioles with edema fluid, the cyanosis testifies volubly to the high degree of anoxemia It is true that not all instances of pulmonary edema in left ventricular failure are accompanied by elevation of arterial pressure. In some cases, the blood pressure falls, presumably, the weakness of the left ventricle more than counteracts the vasomotor stimulation due to the asphyxia The hypertension due to the asphyxia may be very considerable Thus, a man with aortic stenosis was admitted to Mount Sinai Hospital in acute pulmonary edema, deeply cyanotic, bringing up large quantities, of pink, frothy expectoration, and apparently in a critical condition His blood pressure was 212/120 mm He improved with remarkable rapidity after injection of morphine and venesection The next day his blood pressure was 130/80 mm and at no subsequent time did he exhibit hypertension In some patients, the blood pressure rises sharply during each of repeated attacks of pulmonary edema This asphyctic hypertension resulting from pulmonary edema must, of course, be differentiated from the syndrome—occurring especially in acute glomerulonephritis—in which sharp rise in blood pressure is *followed* by left ventricular failure and pulmonary edema.

Incidentally, it may be remarked that the mechanical effects of the respiratory movements are not concerned in elevating the blood pressure in these acute episodes of pulmonary edema or in other instances of heart failure with severe dyspnea Cobet found that during voluntary hyperventilation of high degree, the blood pressure generally falls a little.

Slowing of Blood Flow —Slowing of blood flow through the vasomotor centers presumably tends to stimulate them and thus to

counteract to some extent the hypotensive effect of the diminished cardiac output which produces the slowing (however, see page 168).

Increased Venous Pressure.—Increase in venous pressure due to failure of the right heart, with its resultant rise in capillary pressure, must cause a corresponding increment in the peripheral resistance and therefore in the arterial pressure. In severe right heart failure, this factor might elevate the arterial pressure 10 or even 20 mm. of mercury

Edema.—It has been suggested by Lian and Haguenau[21] that the formation of edema tends to elevate the blood pressure through compressing the capillaries, thus increasing the peripheral resistance. The low blood pressure in chronic nephrosis with its massive edema shows that this factor is insignificant.

Ascites.—The rapid formation of copious ascites may so interfere with the venous return to the heart as a result of compression of the inferior vena cava and perhaps also the portal vein, that the arterial pressure is depressed. Thorington and Schmidt[38] found in dogs that when ascites raises the intra-abdominal pressure to 30 mm. of mercury, the arterial pressure usually falls 5 to 10 mm. of mercury. However, ascites due to heart failure usually forms so gradually that the abdominal wall relaxes and there is little rise in intra-abdominal tension. A much more important circulatory effect of copious ascites is that due to elevation of the diaphragm and consequent displacement of the heart.

Renal Ischemia.—In the light of Goldblatt's work, it might be thought that in heart failure with decreased cardiac output, diminished renal blood flow would tend to elevate the pressure. But apart from rare instances in which embolism of the renal arterial produces hypertension in a patient with heart failure, this conception is purely hypothetical.

Increased Intracranial Pressure.—In right heart failure with high venous pressure the intracranial tension is also elevated (page 277); the pressure of the cerebrospinal fluid in such cases may exceed 350 mm of water. In these cases, it is conceivable, but not proved, that the increased intracranial pressure tends to elevate the arterial tension

Bed Rest.—Bed rest often induces a drop in blood pressure, especially in individuals with hypertension. In many cases of hypertension with heart failure, in which the blood pressure comes down during treatment, the bed rest is undoubtedly a factor.

***Effects of Heart Failure on the Arterial Pressure; High-pressure* Stasis (Hochdruckstauung).**—In view of the diversity and opposing nature of the factors influencing the arterial pressure in heart failure, it might be anticipated that the effects of the latter on the blood pressure would be variable, and such is actually the case.

The changes in arterial pressure during heart failure have been

studied by a number of investigators. The older clinicians thought, more from theoretical considerations than from actual measurements, that heart failure causes the blood pressure to fall, and that with improvement of the heart it rises again. Sahli[34] was the first to make the important observation that in some patients with high blood pressure and circulatory stasis "digitalis is able not only to eliminate the stasis but also, paradoxically, to lower the elevated blood pressure by 30 to 40 mm of mercury" Lang and Manswetowa[13] found that as a rule a break in compensation in cardiac disease is accompanied by a rise in arterial pressure, which falls again as the heart improves. This was especially often the case in mitral disease and the emphysema heart. In chronic myocardial disease, Wolferth[47] observed that the systolic pressure may rise, fall or remain stationary, but that the diastolic pressure almost always fell; only once did it rise as much as 10 mm In mitral disease, Wolferth found a decrease in pulse pressure the most common abnormality. Loschkarewa[23] noted that in 37 of 60 instances of heart failure the blood pressure was elevated during the period of circulatory insufficiency; in only 7 of the cases did the pressure fall strikingly This paradoxical rise in blood pressure was the more pronounced the higher the original blood pressure and the more severe the failure The systolic pressure was more often and more markedly changed than the diastolic Similar observations were made by Meyer and Mullen[27] in a careful study of 35 patients with severe cardiac decompensation. They were treated with rest in bed, digitalis, and opium when needed In 16 cases, the systolic blood pressure fell from 10 to 40 mm as compensation became established, in 12 it was unchanged, and in only 5 did the pressure rise as compensation improved; in the remaining 2, the pressure fell with return of compensation but returned to its original level before the patient left the hospital. Gallavardin[5] also found that as a rule the blood pressure rises during the decompensation of valvular disease (*hypertension asystolique*).

The results of these investigations show—as would be anticipated from the diversity of the participating factors enumerated above—that cardiac failure does not always alter the blood pressure in the same direction. In many cases of valvular disease, hypertension, and chronic pulmonary disease, the blood pressure rises during bouts of decompensation, but in others it falls or is unchanged In the terminal stages of heart failure, of course, the blood pressure falls As far as my observation goes, active myocarditis of rheumatic or other etiology is especially apt to be accompanied by fall in blood pressure, here, there may be complication by peripheral circulatory failure due to the infection. In dynamically significant pericardial effusion, also, the blood pressure generally is depressed, often strikingly so Coronary thrombosis is often accompanied by

a brusque fall in blood pressure; this is so characteristic that in sudden depression of the previously elevated arterial tension, the possibility of coronary occlusion must always be in one's mind. However, exceptionally, the blood pressure rises in the first hours after the occlusion (page 456). Following the occlusion, the blood pressure often remains low indefinitely.

Of special interest is the clinical picture described by Sahli[34] under the term of *Hochdruckstauung*, literally, high-pressure stasis. His description was very cursory and the term has since been applied to different clinical states Apparently, Sahli intended the term high-pressure stasis to indicate only the fact, considered paradoxical at the time, that cardiac failure and high arterial tension can co-exist. He also added the observation, mentioned above, that in such cases the blood pressure may fall when cardiac function improves under the action of digitalis.

Two groups of cases may be included in the category of high-pressure stasis:

1. Patients with pre-existent hypertension in whom the blood pressure is maintained at a high level or even rises as the heart fails.
2. Patients with previously normal blood pressure in whom cardiac failure is accompanied by elevation of blood pressure; here are included:

(*a*) Acute episodes of pulmonary edema with transitory asphyctic hypertension In these, the systolic blood pressure may even exceed 200 mm. (page 233).

(*b*) More protracted episodes of elevation of blood pressure during bouts of decompensation In these the higher pressure may be maintained for weeks and then come down to its previous level as the heart improves. The cases are common, but the elevation is generally only of the order of 10 to 30 mm. of mercury, and therefore can scarcely be designated as hypertension. The best marked examples in my experience have been the failure of the emphysema heart. Most of the cases in which the elevation of blood pressure during decompensation is considerable are elderly individuals, and it may well be that at least some of them have a predisposition to essential hypertension or are in the first phases of this disorder.

The Pulse Pressure.—Decrease in pulse pressure has been considered by some as especially characteristic of heart failure. In mitral stenosis, Wolferth[47] found decrease in pulse pressure the most common abnormality. In arteriosclerotic and hypertensive heart disease, pulse pressure low in comparison to the diastolic pressure is common, but by no means invariable, and even a high pulse pressure may be present when the aorta is very sclerotic. In various types of heart failure, Loschkarewa[23] found that as the heart improves, the pulse pressure most often decreases. In general, the pulse pressure tends to be lower, the more rapid the heart rate,

evidently because the diastolic pressure is elevated by the abbreviation of diastole (page 78).

Blood Pressure Reactions.—As might be anticipated, the blood pressure reactions show some abnormalities in heart failure. Thus, C. Mueller[31] found that the drop in blood pressure which occurs during sleep in the healthy is absent in severe heart failure. And Mortensen[30] observed that the blood pressure is not as well maintained in the erect posture when the heart is insufficient. With an efficient myocardium, he found that the systolic pressure in the erect posture is but slightly lower, up to 8 or 10 mm, than when reclining. On the other hand, Mortensen noted that in cardiac failure the systolic pressure is depressed from 10 to 50 mm on assumption of the erect posture The diastolic pressure rose slightly in the erect posture in both the healthy and those with diseased hearts. Mortensen suggested the comparison of the blood pressure in the erect and reclining posture as an index of cardiac efficiency. However, I have several times observed considerable drop in arterial pressure in the erect posture in individuals of asthenic habitus but no heart disease, the fall in arterial pressure in such persons is probably due to decreased venous return rather than cardiac weakness

Peripheral Circulatory Failure.—The arterial pressure in shock is discussed in Chapter XXXI.

ALTERNATION OF THE PULSE

In a patient with an enlarged and failing left ventricle, apparently on the basis of hypertension and coronary sclerosis, Traube[33] observed "a sequence of high and low pulses, occurring in such a manner that a high pulse regularly follows a low pulse, and that this low pulse is separated from the following one by a shorter pulse than from the preceding high pulse" To this phenomenon Traube applied the term *pulsus alternans*, though some authors prefer to designate it as alternation of the heart and thereby indicate the origin of the variations in the strength of the pulse Traube's description of the weak beat as closer to the succeeding than to the preceding stroke is important, it serves in general to differentiate the true pulsus alternans from the sequence of strong and weak pulses due to regularly recurring extrasystoles (pulsus bigeminus), in which the weak beat is usually closer to the preceding pulse.

Following Traube's clinical observations, alternation was studied in the surviving cold-blooded heart in the course of Gaskell's[7] classical work. Since then, alternation has been subjected to extensive clinical and experimental investigation, which is discussed in detail in the monographs of Gravier,[8] Kisch,[12], and Poumailloux.[33]

Clinical Description of Pulsus Alternans.—When the alternation is very marked, it is immediately detected on palpation of the radial pulse. There is a succession of strong and weak beats, the rhythm being either regular or the weak beat closer to the *following* strong beat Isolated cases have been observed in which the alternation was so extreme that the pulse at the wrist was halved to the palpating finger The alternation may be more obvious in one artery than another, thus, in Traube's original case the alternation could be detected at times in the carotid when it could not be felt in the radials For the detection of the pulsus alternans, Windle[44] advises that the palpating finger be applied lightly when the arterial tension is low and firmly when it is high. An artifice that is sometimes of help is the bimanual palpation suggested by Gallavardin and Gravier [6] The brachial artery is gradually compressed with one hand while the radial pulse is palpated with the other.

However, cases of alternation so marked as to be obvious on simple palpation are rare, and those who confine themselves to this method will overlook most instances of the pulsus alternans. Much more often, alternation is first detected by careful observation during the measurement of the blood pressure If the cuff is inflated well above the systolic pressure and the air let out slowly, the first sounds heard correspond to only half the heart beats; this is the systolic pressure of the strong beats. Continuing the deflation, the sounds corresponding to the weak beats appear when the systolic pressure of the latter is reached. The differences between the systolic pressures of the feeble and the strong beat may range from a few to more than 40 mm Hg, although the higher values are very rare. These findings can often be confirmed by palpation of the radial pulse during the compression. Morris[29] states that the intensity of the sounds over the brachial artery usually alternates all the way to the diastolic pressure This has been very exceptional in my experience

The most sensitive method of detecting alternation is by means of the sphygmograph. The pulse tracing reveals alternation of a degree too slight to be evident by the above-mentioned clinical procedures. It is by means of the sphygmograph that the highest percentages of instances of pulsus alternans have been detected (page 87) The strong beats rise higher than the weaker ones. Moreover, as pointed out by Wenckebach and Winterberg,[40] the weak beats may start from a higher footpoint than the strong ones; they attribute this to the fact that the strong beats leave the arteries better filled. There may also be alternation in the form of the plateau, the location and forms of the dicrotic wave, etc The sphygmograph also brings out the diagnostically important point (for differentiation from the bigeminy of extrasystoles) that the

beats are equally spaced or the small beat is closer to the succeeding large beat. As a rule, the delay in the small pulse is the greater the more marked the difference between the height of the small and large pulses The mechanism of the retardation of the small pulse is discussed below.

In some instances, alternation is continuously present, but in others it appears only under special circumstances. Very often alternation can be brought out or intensified by having the patient exercise. I have frequently employed this artifice successfully, especially in hypertension The blood pressure cuff should be left in place during the exercise so that auscultation of the brachial artery can be begun immediately after the patient comes to rest The other circumstance which often brings out alternation is a premature contraction, the inequality of the pulses may be present for only a few beats after the extrasystole. Lewis[16] points out that a premature contraction may be evoked by holding the breath, and alternation thus rendered manifest

The Heart in Alternation.—Inasmuch as the immediate mechanism of the pulsus alternans is that the left ventricle expels larger and smaller volumes of blood in alternate contractions, it might be thought that the evidences of alternation on examination of the heart would be very striking Such is actually the case in the experimental animal where the heart is exposed or excised, but in most clinical cases the cardiac signs of alternation are characterized by their paucity and may indeed be indiscernible by all the usual methods of examination In fact, Windle and Laubry[14] did not observe *any differences in the heart sounds corresponding to the* alternating beats. On the other hand, Morris found alternation in the intensity or pitch of the heart sounds or murmurs in 7 of 19 patients with constant pulsus alternans. Mackenzie[24] long ago pointed out that alternation of a systolic murmur is especially apt to occur. By means of graphic records, Cossio[4] and his associates demonstrated concordant alternation of the first sound in all of seven instances of pulsus alternans, alternation of the second sound was present in only 4 of the patients.

Direct evidence of the alternation of the cardiac contractions has been obtained by radioscopic methods Meyer and Levy[26] mention briefly that they accomplished this, apparently with the fluoroscope. Scherf and Zdansky[35] have published the roentgen kymogram in a case with pulsus alternans which exhibits the alternation of the amplitude of contraction of the left border of the left ventricle.

The cardiogram may exhibit the alternation very clearly. However, there are also instances of well-marked alternation of the pulse which do not reveal the alternation in the mechanical tracing of the apex beat Alternation in the cardiogram does not necessarily

correspond to that of the pulse; thus, Windle and Hering[9] have published cardiograms, the former in clinical alternation and the latter in the dog, from different areas in which the alternation in the height of the individual ventricular waves was the reverse of that of the pulse The explanation lies in the fact that the excursion of the mechanical tracing from all areas of the precordium is not necessarily a measure of the volume of blood expelled by the heart. Perhaps the most important point revealed by the cardiogram is that in almost all instances the cardiac contractions are absolutely regular despite the fact that the small pulse wave is usually delayed at the wrist. This shows that the retardation of the small pulse beat is not due to a delay in the onset of the corresponding ventricular systole but to a greater interval between the time of occurrence of the weaker cardiac contraction and its pulse beat than that between the stronger systole and the corresponding pulse. In alternation produced with glyoxylic acid in the rabbit, Hoke and Rihl[11] found that the weak pulse was delayed 0 073 second, while the strong one was delayed 0.044 second. Evidently, the pulse of the weak systole is transmitted more slowly; there may also be a delay in the opening of the aortic valve by the weak beat. On rare occasions, a delay in the weak cardiac systole itself has been observed (Lewis and Mathison[20] and others).

Perhaps the most remarkable feature of the *electrocardiogram* in patients with pulsus alternans is that it most often fails to show any trace of alternation. There are, however, instances in which alternation is manifested in the electrocardiogram. Most often, this consists in alternation in the amplitude of the *T* wave, but the *R* or any of the other deflections may be similarly affected, and rarely alternation in the form of some part of the electrocardiogram is present. The larger wave in the electrocardiogram may correspond to either the large or the small pulse beat Lewis[17] long ago pointed out that there is no correspondence between the electrical and mechanical manifestations of alternation; he stated that there may be alternation in the electrocardiogram when none is discernible in the pulse. On the basis of these facts, Poumaillaux,[33] Condorelli,[3] and others have endeavored to differentiate electrical (affecting the excitation wave) from mechanical (affecting the contractile force) alternation of the heart As a most striking instance of electrical alternation, Condorelli mentions the rare instances in which the electrocardiogram exhibits alternation of right and left bundle-branch block; this has been observed especially during attacks of paroxysmal tachycardia As another example of electrical alternation, Condorelli cites instances of auricular fibrillation in which the *R* wave alternates in height although there is no regularity about the duration of the preceding diastoles. Despite these facts, Kisch[12] denies the justification for fundamental differ-

entiation between electrical and mechanical alternation; he holds that it is based merely on the greater predominance of one or another symptomatic manifestation of the same underlying phenomenon.

In a few instances, the first due to Volhard,[39] evidences of alternation of the auricle have been observed in the auricular wave of the phlebogram or cardiogram, in some instances these have been secondary to ventricular alternation, but in others there seems to have been independent auricular alternation (See Wiggers[43] and Pezzi and Donzelot [32]) Alternation of the *P* wave has also been observed by Wiggers and others

The inequality of the cardiac contractions in alternation occasions no subjective sensations.

Occurrence of Alternation.—The pulsus alternans was formerly considered a rarity. This is true of the manifest variety, immediately detectable on palpating the pulse But alternation is not so rare when more precise methods are used Thus, with the sphygmograph White[41] demonstrated alternation in no less than 71 of 300 cardiac and cardiorenal patients. Sixty-six of the 210 patients with cardiac decompensation had alternation. In the 71 instances of alternation, it was constantly present in 15, only after premature beats in 55, and was of a phasic type in the other one.

The conditions under which alternation appears clinically are those in which the heart is overtaxed. This may be due to disease of the heart muscle, as in coronary sclerosis, to an increase in the work required, as in hypertension, or to diminution in the diastolic rest period, as in paroxysmal tachycardia However, it is to be emphasized that factors other than heart failure also enter into the pathogenesis of the pulsus alternans This is indicated by the fact that the most severe heart failure is by no means always accompanied by alternation. I have often failed to detect the pulsus alternans in patients dying of classical asystole, even though I sought for it carefully with the sphygmomanometer. In the large majority of instances of heart failure in valvular disease, alternation never appears to the very end On the other hand, it may occur in well-marked fashion in the hypertensive or arteriosclerotic heart, or during paroxysmal tachycardia, while the patient is able to get about. I have several times detected alternation in hypertensive individuals who had been keeping at their occupation. Interestingly enough, as has been noted by previous observers, the alternation in such patients may disappear when heart failure becomes more severe. Indeed, it seems to be the rule that pulsus alternans disappears in the terminal stages of asystole. Evidently some coefficient in addition to heart failure enters into the pathogenesis of alternation, the matter will be discussed further below, where it

will be pointed out that little is actually known of the nature of this factor.

The clinical conditions in which alternation is most often observed are hypertension and tachycardia.

The vast majority of instances of pulsus alternans, especially when well marked, occur in patients with arterial hypertension. This was the case in 18 of Poumaillaux's 21 patients with alternation and in 15 of Loeffler's[22] 16. Most often, these hypertensive patients with pulsus alternans present evidences of left ventricular insufficiency; there may or may not also be right heart failure. I have seen alternation of 20 mm. disappear in a hypertensive when the right heart failed Alternation has been observed to diminish or disappear when elevated blood pressure is lowered with amyl nitrite (Kisch) or acetylcholine (Poumaillaux). Most hypertensive patients with pulsus alternans present clinical or electrocardiographic evidences of myocardial damage attributable to coronary arteriosclerosis, and this is presumably true in practically all. Much more rarely, alternation occurs in coronary artery disease in the absence of present or past hypertension Peculiarly enough, pronounced alternation of the pulse is a rarity in recent myocardial infarction (Boucomont,[1] Poumaillaux, own observations) This is the more puzzling because Lewis[18] long ago showed that alternation of the heart commonly appears in experimental coronary occlusion. In Lewis' experiments there was marked tachycardia, to which the alternation might be attributed However, in experiments on perfused canine and human hearts, Kisch[12] showed that the alternation is a direct consequence of the disturbance in the nutrition of the area supplied, for occlusion of the left coronary was followed by alternation confined wholly or solely to the left ventricle, and that of the right coronary by alternation of the right ventricle. I have not observed alternation of the pulse in peripheral circulatory failure

Next to arterial hypertension, the pulsus alternans is most commonly associated with tachycardia In the vast majority of instances of clinical alternation, the heart rate is accelerated. Experimentally, it has been demonstrated in a variety of ways (see Kisch) that in a heart predisposed to alternation by exhaustion or other metabolic changes, the alternation can be brought out or intensified by accelerating the pulse rate and, on the other hand, caused to disappear or diminish by slowing the heart. The same is true in clinical medicine Quite often, acceleration by exercise of the heart weakened by coronary sclerosis or other cause serves to bring out transitory alternation, which vanishes as the heart slows However, the outstanding example of alternation due to tachycardia is seen in paroxysmal tachycardia. In these patients, there may be marked alternation during the attack even though there are no

peripheral evidences that the heart is failing. When the attack is over, the alternation disappears Occasionally, alternation clears up during digitalis therapy; the slowing of the heart is probably concerned.

In addition to these two classes of cases—the one with hypertension or coronary disease and the other with paroxysmal tachycardia—which make up the vast majority of instances of alternation, the pulsus alternans is observed in very rare cases of rheumatic and thyrotoxic heart disease, as well as in the cardiac failure of pneumonia and other infections It is rather remarkable that alternation should be so rare in the thyroid heart despite the pronounced tachycardia usually present

There are a few observations on record in which alternation was produced in humans by digitalis A clear example is that reported by Windle,[45] in which the administration of digitalis to a woman with tachycardia and nervous symptoms, but neither Graves' disease nor heart failure, resulted in alternation following the extrasystoles due to the digitalis.

A remarkable observation is recorded by Mackenzie, which concerned alternation during renal colic, though it was present neither before nor after.

In *animal experimentation*, alternation of the heart is often encountered and readily produced It has been known since the classic studies of Gaskell[7] on the frog's heart, that when the surviving heart becomes exhausted as a result of protracted contraction or deficient nutrition, alternation commonly develops The alternation may affect only the apical or basal portions of the ventricle, or it may be more widespread. Alternation has also been observed in surviving strips of heart muscle It was mentioned above that alternation can be produced by obstruction of a coronary artery. Acceleration of the heart either by direct stimulation or through the nerves may also bring out alternation. A number of chemicals have been shown to produce alternation. Among them are the digitalis bodies, of which antiarin has been especially used in the experimental study of alternation. Glyoxylic acid has also been found to produce very marked alternation

Pathogenesis of Alternation.—The remarkable phenomenon consisting in alternation of a larger and a smaller stroke volume of the left ventricle in the absence of any aberration of rhythm has naturally evoked attempts at explanation These have been based not only on clinical observation but also on experimental studies The latter have been facilitated by the ease with which alternation is produced in either the cold or the warm-blooded heart Nevertheless, it must be admitted that as yet the fundamental pathogenesis of alternation is largely obscure It is, indeed, quite possible that

there exist pathogenetically distinct varieties of alternation, a view to which most recent investigators (*e g*, Wiggers[42]) incline.

The conditions under which alternation is encountered in clinical and experimental work immediately suggest that the phenomenon is in some way connected with cardiac failure This is another way of saying that alternation is a manifestation of encroachment on the factor of safety of the heart, *i. e.*, that the heart is laboring close to its maximum capacity at the moment, be this a result of increase in the rate or load, of qualitatively or quantitatively inadequate blood supply, or of intrinsic disease of the myocardium. However, such an "explanation" of alternation as a manifestation of heart failure meets with difficulty in elucidating the fact that alternation is most often absent in certain varieties of heart failure, for example in valvular disease, as well as the common observation that alternation generally disappears in the terminal stages of heart failure, although the heart is then less competent than when the alternation was present. In addition to heart failure, therefore, there must also be accessory factors in the pathogenesis of alternation which are present in only some conditions of cardiac embarrassment and then lead to alternation, and which generally vanish in the terminal stages of asystole with the disappearance of the alternation

In a broad way, there have been two schools of thought concerning the pathogenesis of clinical alternation:

1. Those who consider the alternation as due primarily to alternate increase and decrease in the strength of the cardiac contraction.
2. Those who believe that while diminution in the functional capacity of the myocardium is an essential prerequisite, the actual alternation is evoked by appropriate dynamic conditions of the circulation which alternately increase and decrease the filling of the heart and therefore its output.

Cardiac Factors in Alternation.—Since the pioneer observations of Gaskell,[7] there has been no doubt that alternation can be due entirely to changes in the myocardium without the intervention of extracardiac factors. This is proved by repeated observations of alternation in the bloodless heart and even in rings of cardiac muscle. Moreover, Gaskell observed in the frog's heart that alternation may affect only part of the ventricle, the basal part contracting at each beat but the apex only at alternate beats—"partial alternating asystole" In other instances, observation of the exposed heart indicates that it is not a localized area of the organ that fails to contract at alternate beats but that every second contraction is weaker throughout the heart—"total alternating asystole," or really hyposystole. In the latter event, the defective fibers may be diffusely distributed throughout the alternating chamber.

The explanation of these observations that naturally offered itself to Gaskell and his followers was that alternation is due to the nonparticipation of some of the heart muscle fibers in alternating

contractions. Following Mines,[28] it is now generally thought more probable that when alternation is present some fibers do not contract in either the large or the small beats, but that the number falling out is greater in the small beat. According to this view, both the larger and the smaller beats in alternation are abnormal, a conception which helps to explain certain of the above-mentioned discrepancies between the electrical and the mechanical changes.

No entirely satisfactory explanation for the falling out of certain fibers at alternate contractions has yet been offered. Gaskell attributed it to decrease in irritability, while other investigators have incriminated deficient contractility or conductivity. Kisch is of the opinion, and brings experimental evidence to support his view, that all the functions ("bioenergetic properties," as he terms them) of the fractions of the myocardium which fall out are depressed. The most widely held conception is that the refractory period of the fibers in question is increased as a result of the underlying disease (deficient blood supply, overwork, etc) so that they fail to contract at every beat, and only respond to every second or rarer stimulus, being enabled to do so by the longer rest. This conception of alternation as due to prolongation of the refractory period of certain fibers accords very well with the fact that the appearance of alternation is favored by acceleration in rate, and that alternation may appear during paroxysmal tachycardia in a heart which is apparently functionally competent But it is to be emphasized that the explanation is as yet little more than hypothetical and indeed has little meaning until more is known of the biochemical basis of the refractory period even under normal, let alone diseased, conditions

Rôle of Extracardiac Factors in Alternation.—Of late years, the significance of extracardiac factors for the pathogenesis of the pulsus alternans has been stressed, especially by Wenckebach[40] and more recently by Wiggers[42] and Poumailloux[33] It has long been known that under many circumstances there is a direct relation between the stroke volume of individual beats and the length of the preceding diastole. Three factors may be concerned in this proportionality: The longer the preceding diastole, (1) the greater the filling of the heart because more time is allowed for venous return, (2) the lower the pressure in the aorta because the arteries have more time to empty, and (3) perhaps the succeeding systole is more powerful because of the longer rest period.

The dynamic considerations explain very plausibly why premature contractions are so often followed by alternation of varying duration in the hypodynamic heart. The premature contraction is followed by a prolonged diastole (compensatory pause) As a result of this prolonged diastole, the three factors mentioned above operate: aortic pressure is lowered, the filling of the heart is increased, and its recuperation is greater. The consequence is that

the next systole expels a large volume of blood. However, as a result of the larger stroke volume, aortic pressure is raised, the volume of blood remaining in the ventricle is small (Wiggers), and the muscle is more fatigued. The consequence is that the succeeding systole expels a smaller volume of blood This sequence may be repeated a number of times, the difference between the large and small beats gradually becoming less

Likewise, Wenckebach points out that these hemodynamic considerations explain why acceleration in rate favors so greatly the development of alternation. For the filling of the ventricle occurs almost entirely in the first part of diastole (page 293) Since diastole is greatly shortened by tachycardia, slight variations in rhythm will impinge on this period of rapid filling and thus affect the output of the heart much more markedly when there is tachycardia Hence, premature contractions are more apt to be followed by alternation when the heart is rapid Experimental verification of these conclusions was obtained by Wiggers In a variety of experiments, he showed that a prolonged diastole (such as follows a premature contraction) is followed by alternation when the heart rate exceeds a critical level of about 140 per minute.

These studies indicate quite clearly that *one* hemodynamic condition which favors the production of alternation is a prolonged diastolic pause interrupting an accelerated heart rate Indeed, Wenckebach is of the opinion that such a mechanism is operative in all instances of human alternation. He maintains that the rhythm of the heart is never absolutely regular; that minute irregularities are the rule and not the exception, and that such irregularities, acting in the presence of hypertension or tachycardia, bring on alternation by the hemodynamic mechanism just discussed. This is probably true in the instance of alternation following premature contractions But in the case of continuous alternation, there is no evidence of the rôle of irregularity of rhythm, which is indeed hypothetical Here, the causes of the alternation seem to reside primarily in the defect of the myocardium itself, with extracardiac hemodynamic factors playing only a secondary and accessory rôle. We have seen that the most widely held conception of the nature of the myocardial defect is that it consists in the deletion of the contractions of individual elements of the myocardium quantitatively so spaced as to result in alternately weaker and stronger systoles; that this "explanation" contains a large germ of assumption has already been sufficiently emphasized.

Although this obscure myocardial disturbance is of primary importance for the pathogenesis of alternation, the secondary hemodynamic factors are likewise very significant. Indeed, it seems to be most often these hemodynamic coefficients which serve to convert potential into manifest alternation. This is illustrated by the cases in which alternation can be detected only after the long

diastolic pause of an extrasystole or only after the heart has been accelerated by exercise. And likewise alternation may be caused to disappear by removing some secondary coefficient, as when the heart rate is slowed or the blood pressure lowered with accompanying abatement of alternation

Prognostic Significance of Alternation.—The pulsus alternans has been regarded as a harbinger of imminent evil ever since Mackenzie's observation that his patients with alternation all succumbed within a few years. "It is the faint cry of an anguished and fast failing muscle, which, when it comes, all should strain to hear, for it is not long repeated A few months, a few years at most, and the end comes" (Lewis). Twenty-five of White's[41] 71 patients with alternation demonstrable in the sphygmogram died within ten months of the finding

Of the evil prognostic significance of *continuous* alternation present when the patient is at rest, there can be no doubt. It seems safe to say that a large majority of such patients—who are usually sufferers from hypertension and coronary sclerosis—succumb within two years of the finding of the pulsus alternans However, there are also exceptions, like all other signs or symptoms, the pulsus alternans is not prognostically infallible. I saw a man with hypertension, coronary sclerosis, and probably an aneurysm of the left ventricle who had had alternation for three years and nevertheless was able to get about when I last saw him The literature contains a number of instances of well-marked alternation lasting for many years Thus, Mackenzie mentions a man with alternation of fourteen years' duration, and Laubry and Routier[15] instances of eight and eleven years

It appears that the more marked the alternation, *i. e.*, the greater the difference between large and small pulses, the more serious the prognosis. In fact, minimal alternation of a few millimeters of mercury seems to have comparatively little prognostic significance, although it generally accompanies other evidence testifying to serious myocardial damage. In a general way, it has been found that alternation occurring in the presence of accelerated heart action is of less serious prognostic significance than in the unusual cases in which the heart is slow. If the alternation clears up on digitalis, it appears to convey no prognostic implications other than those furnished by the accompanying clinical features, a number of interesting cases of this type have been published by Windle.[46]

Similarly, the rather common alternation that occurs only after a premature contraction appears to be of little help in prognosis. I also have the impression that alternation detectable only after exercise does not necessarily carry evil prognostic implication At least, I have several times observed such post-exertional alternation in young patients with rheumatic heart disease who were in fairly good shape and attending school

Alternation occurring only during paroxysmal tachycardia is considered by Mackenzie and others to be of no considerable significance. I also observed a man who had readily palpable alternation during his attacks, but was well in the intervals.

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CHAPTER VI

THE VENOUS PRESSURE AND PULSE

Two hundred years ago, Stephen Hales[26] measured the venous pressure* in the horse and sheep by inserting a glass tube into the jugular vein and observing the height to which the blood rises, a method in use today. The venous engorgement that often enables the detection of an insufficient heart at the first glance has been familiar to clinicians for over two centuries. The measurement of venous pressure in the experimental animal and the observation of engorged veins in heart disease are thus very old. Nevertheless, until recent years comparatively little attention was paid to the quantitative investigation of changes in venous pressure in circulatory disease. This neglect was largely the result of the prevalent conception that the veins function as passive conducting tubes and that changes in the blood content of the veins and the venous pressure are merely the reflection of alternations in the activity of the other organs of circulation From this point of view, beginning at the end of the last century, graphic methods were applied to the study of the venous pulse, from which most of our knowledge of cardiac arrhythmia originated But the measurement of the absolute height of the venous pressure was not considered of significance for the clinicians Realization of the clinical importance of the venous pressure had to await the demonstration by Henderson, Starling, and other physiologists of the active rôle of the venous return to the heart in the regulation of the circulation (See Chapter XVIII.) Since then, the venous pressure has been studied under various pathological circumstances and much information of value at the bedside acquired Comprehensive monographs on venous pressure in disease have been published by Eyster,[17] Villaret, Saint-Girons and Justin-Besançon,[60] and Pogany [54]

* The term venous pressure will be used in the following to connote the pressure in the peripheral tributaries of the venæ cavæ, the only venous pressure that is measured by the clinician Usually, the pressure is measured in the antecubital vein, exceptionally, when mediastinal or abdominal pressure is suspected, in the femoral vein It is unfortunate that no method is available for the clinical measurement of the pressures in the pulmonary and portal circuits Recently, Staudacher[66] has attempted to measure the pressure in the left auricle, which would orient us concerning the pressure in the pulmonary veins His technic consists in the introduction of Frank capsules into the esophagus at the level of the left auricle and the measurement of the pressure by oscillometry He found an average left auricular pressure in health of 25 to 35 mm of water The left auricular pressure was elevated to 60 or 70 mm of water in a patient with arterial hypertension and one with aortic stenosis There was slight elevation of pressure in an instance of mitral stenosis and more in a case of mitral regurgitation but none in an individual with aortic regurgitation

The great importance of the venous pressure for clinical medicine arises from the fact that *the venous return to the heart is the immediate determinant of the volume of circulation, i e, of the cardiac output.* Since the heart functions as a force pump, the cardiac output is determined by the volume of blood forced into the right auricle by the pressure at the mouths of the venæ cavæ; the heart cannot compensate for low venous pressure and consequent small venous return by actively aspirating blood from the great veins as would a suction pump. In other words, the heart cannot discharge more blood per minute than the veins actively force into it; diminution *in venous return entails corresponding fall in volume of circulation.* On the other hand, increase in venous return, if the heart is functionally competent, results in correspondingly heightened output It has been seen above that this accommodation to greater venous return is accomplished (1) through increased output per stroke resulting from larger diastolic filling, and (2) through acceleration in rate which the augmented venous return perhaps initiates through the greater pressure in the great veins and heart (Bainbridge reflex)

THE REGULATION OF THE VENOUS PRESSURE

Before proceeding to the discussion of the normal venous pressure, its measurement, and its aberrations in individual diseases, a brief general discussion of the factors concerned in the regulation of the venous pressure may not be amiss. These may be considered in five general categories:

1 The rate of entry of blood into the veins.
2 The tone of the veins.
3. The circulating blood volume.
4. The extravascular aids to venous flow.
5. The activity of the heart

The Rate of Entry of Blood Into the Veins.—The tension under which the blood enters the venules is the remnant of the pressure due to ventricular systole that remains after overcoming the frictional resistance in the arteries and capillaries Landis[38] found that in the venous limb of the capillaries at the base of the finger nail (supported at the level of the suprasternal notch), the pressure averages about 15 cm of water This is the pressure under which the blood enters the venules on the dorsum of the finger; possibly, of course, the initial venous pressure differs in other parts of the body, although it is probably of the same order of magnitude Dilatation of the arterioles or capillaries elevates the tension under which the blood enters the venules of the territory in question, while arteriolar or capillary constriction diminishes the initial venous pressure. This is illustrated by the observations of Lewis and Haynal,[42] who found that when vasodilatation is produced by heat,

the pressure in the venules may exceed 100 cm. of water; they also observed rise in the venular pressure to about 80 cm. of water following the application of histamine Contrariwise, Landis found that when the minute vessels are constricted by cold, the pressure in the venules falls. Similar observations have been made with amyl nitrite and other drugs that alter the caliber of the arterioles and capillaries. More rapid entry of blood into the venules as a result of peripheral vasodilatation doubtless plays a part in the increased venous pressure in the large veins during exercise, although the main factors are the massaging action of the contracting skeletal muscles and the displacement of blood into the extremities from the splanchnic region

Accelerated entry of blood into the veins is of little significance in causing elevation of the general venous pressure in disease. It is true that Boas[5] has demonstrated that the so-called capillary pulse in aortic regurgitation is really due to pulsation in the venules, but this does not prove that the pressure in the venules is increased, the pulsation of the blood stream in the venules may be due entirely to a diastolic fall in the venular pressure The venous pressure as measured in the antecubital veins is not generally elevated in compensated aortic regurgitation In Graves' disease, fever and anemia, the minute volume of blood entering the veins is increased, but this is balanced by a corresponding elevation in the work of the heart, so that the venous pressure remains unaltered as long as the heart is functionally competent

Contrariwise, diminished entry of blood into the veins tends to lower the venous pressure Thus, Pogany,[54] Villaret,[60] and others have reported low venous pressure in some cases of acute glomerulonephritis, which they attribute to the constriction of the peripheral vessels that produces the high blood pressure In support of this view, Pogany found that in such cases moderate degrees of heat, insufficient to influence the venous pressure in health, elevated the latter. In cardiac failure, the diminished *vis a tergo* may result in less blood entering the veins from the capillaries per unit of time, but this factor is usually far more than counterbalanced by the elevation in pressure in the venæ cavæ due to the inadequate emptying of the heart, so that characteristically the venous pressure rises In peripheral circulatory failure the low venous pressure is due to diminution in circulating blood volume, one of the effects of which is a decrease in the volume of blood entering the veins.

The Tone of the Veins.—The veins possess a muscular coat, variations in the tone of which determine the caliber of the vessel. Investigations of recent years have shown that such changes in the tone of the veins, either generalized or limited to veins of special areas, are among the most important means of control of the venous return to the heart and therefore of the volume of circulation. The

tone of the veins is regulated by physical, chemical and nervous mechanisms; the point of attack of the latter may be either central or peripheral.

The chemical control of the veins has been extensively investigated. Details will be found in the extensive review of Pogany,[54] and in the studies of Donegan[15] and Lewis.[40] The following are some of the most important results from the point of view of the relation of the tone of the veins to the regulation of the circulation as a whole. Epinephrin is a powerful venoconstrictor, exercising this action along the entire course of the veins (See page 66 for exception) On the other hand, while histamine constricts at least many of the larger veins (notably in the liver, see page 66), it dilutes the venules (Dale and Richards,[14] Dale and Laidlaw,[13] Lewis[40]) to a varying degree in different territories. Pituitrin constricts the veins. In some regions acetyl choline has a similar action, although Courland and Kahane[12] have observed dilatation of the retinal vein The studies of Donegan,[15] Beckmann,[4] and *Gollwitzer-Meier and Bohn*[24] *have shown that the tone of the* veins is affected by asphyxia, the administration of carbon dioxide, and changes in hydrogen-ion concentration in general Increase in hydrogen-ion concentration constricts most veins by local action, although Beckmann found that the mesenteric veins are not affected. According to the observations of Beckmann, this venoconstriction is produced by very small increases in hydrogen-ion concentration within the physiological limits of acidity, and is doubtless of much significance in the regulation of the circulation

The nervous control of the tone of the veins has also been subject to much study Thompson[59] long ago showed that stimulation of the sympathetic constricts the superficial veins Donegan found that reflex vasoconstriction follows stimulation of the sciatic nerve. Gollwitzer-Meier and Bohn showed that increase in the carbon dioxide content of the blood produces vasoconstriction through the medium of the venomotor nerves, which are included in the sympathetic fibers It seems likely that this effect is due to changes in the acidity of the blood flowing through the vasomotor centers Gollwitzer-Meier[22] and Fleisch[19] have found that a fall in blood pressure within the carotid sinus induces constriction of the veins, while a rise in carotid sinus pressure dilates the veins. From these different observations it is obvious that, as one would anticipate, the central control of the arteries and veins is closely coordinated. In the past, clinicians have concentrated their attention too narrowly and exclusively on the vasomotor control of the arteries. However, the regulation of the venous return to the heart is of equal significance for the problem of the pathological physiology of the circulation, a fact which is being more and more appreciated since the pioneer studies of Henderson[27] on the venopressor mechanism

Vasomotor changes in the arteries and veins complement one another, as well as the activities of the heart and capillaries, so that the circulation may function efficiently in meeting the ever-varying demands of metabolism; and it is probable that the necessary correlations are accomplished to a considerable extent through the intermediacy of the central nervous system. Whether or not there are anatomically distinct arteriomotor, venomotor and capillaromotor centers is a problem that awaits solution.

Changes in the tone of the veins play their part in the regulation of the circulation in two ways: (1) By altering the resistance to blood flow through the veins, and (2) by varying the capacity and consequently the blood content of the veins. The great importance of this differentiation between resistance and capacity in elucidating the significance of venomotor changes has been especially emphasized by Hess.[29]

Changes in Venous Resistance.—In general, the resistance to blood flow along the veins is but slight when compared to that encountered in the arterial tree. This is indicated by the fact that the pressure in the venules is only of the order of 15 cm. of water, which suffices, with the aid of respiration and the contraction of the skeletal muscles, to return the blood to the heart. In fact, this small initial pressure is *per se* adequate to bring the blood back to the heart, for the circulation continues when respiratory aid is practically eliminated by opening the thorax and maintaining artificial respiration, and muscular contractions are prevented by the administration of curare. The pressure gradient from the capillaries to the heart is only about one-sixth of that from the heart to the capillaries. The anatomical explanation of this small resistance to blood flow along the veins is, of course, that the cross-section of the venous tree is much greater than that of the arterial tree at a corresponding level. Hess points out that as a result of the large cross-section of the veins, considerable degrees of venous dilatation or constriction result in comparatively slight changes in *resistance* to blood flow.* However, as will be seen on page 101, the corresponding changes in *capacity* of the veins are of great significance. The state of affairs in the veins, as Hess points out, is quite the opposite of that in the arteries, which have a relatively small cross-section, and whose important rôle in the regulation of the circulation is performed through alterations in resistance and not in capacity.

Localized Venous Throttle Mechanisms.—In the foregoing, it has been seen that *generalized* alteration in resistance to blood flow

* It is possible that this does not apply to the pulmonary circuit and that the pulmonary venules play an important part in regulating the resistance to blood flow through the lesser circulation. Mautner and Pick[47] and Luisada[48] have found that histamine and peptone constrict the pulmonary venules, which indicates the possibility that this mechanism may be concerned in the pulmonary phenomena of the allergic reaction.

along the veins is not of primary importance for the regulation of the volume of circulation On the other hand recent work has shown that changes in the resistance to blood flow by the veins draining *individual* vascular territories as a result of dilatation or constriction are of the utmost significance for the regulation of the circulation. Such variations in the tone of the veins enables them to exert a throttle-like action which controls the volume of blood poured into the general venous circulation from the territory in question. Perhaps the most important of such local venous throttle mechanisms is that of the hepatic veins, which is discussed in detail on page 65. By constriction of the hepatic veins—according to Dale[2] and his associates close to the caval orifices—blood is dammed back into the liver and portal radicals. Because of the capacity of the vascular territory draining into the hepatic veins, a very considerable portion of the total blood volume can be held back from the general circulation. This serves to diminish the pressure in the other tributaries of the venæ cavæ and to lessen the *venous return to the right heart, with consequent diminution in* cardiac output The hepatic throttle mechanism functions in some forms of experimental shock in animals, but whether this also occurs in humans remains to be determined (page 67). It is possible, but not proven, that the mechanism also operates in some instances of right heart failure in which the liver is greatly swollen with but little rise in venous pressure On the other hand, the opening of the hepatic vein throttle tends to increase the venous pressure and the return to the right heart This mechanism presumably is brought into play in accelerating the circulation during exercise, for Dale and his co-workers have shown that epinephrin relaxes the hepatic veins (page 66)

A similar throttle mechanism has been described by Pogany[53] in the veins of the skin. He observed in some cases of right heart failure that the larger veins on the back of the hand were visibly and palpably contracted, and that this contraction could be relaxed by application of warm water to the extremity, with this relaxation, the pressure in the veins in question fell. Inasmuch as the venules of the subpapillary plexuses of the skin were distended with blood, Pogany considers that the combination of contracted veins and distended venules forms a throttle mechanism analogous to that *of the liver. When the veins are contracted, blood is retained in* the venules of the skin and thus kept from returning to the heart, while when the veins relax, the venous return to the heart is increased. In view of the enormous capacity of the subpapillary venous plexuses, which function as blood reservoirs (page 64), the throttle mechanism resulting from the constriction or dilatation of the larger veins of the skin may be of considerable importance in the regulation of the venous return to the heart and consequently

of the cardiac output. The fact that Pogany was able to demonstrate the contraction of the large veins of the skin, especially in association with right heart failure, may indicate that the mechanism is called into play to protect the weakened right heart from the inflow of a larger volume of blood than it is able to master.

Associated with the action of venous throttle mechanisms, there may also be a synergistic alteration in the capacity of the capillaries and venules of the affected area. Thus, in right heart failure the contraction of the larger veins of the upper extremity was found by Pogany to be associated with dilatation of the subpapillary venules so that, functionally speaking, a blood reservoir was formed. The same principle is illustrated in the effects of histamine and epinephrin on the vessels of the liver Histamine constricts the larger hepatic veins and dilates the minute vessels of the liver. Obviously, these two actions supplement one another in retaining blood in the liver and diminishing the return to the right heart. On the other hand, epinephrin relaxes the large hepatic veins and constricts the small vessels, thus forcing blood out of the liver and increasing the return to the right heart

Changes in the Capacity of the Veins —The capacity of the veins is much greater than that of the arteries It is immediately obvious that the cross-section of the two venæ cavæ plus the coronary sinus at their openings into the heart is much greater than that of the root of the aorta. Peripherally, the disproportion between arterial and venous capacity is even greater. The result of this large capacity of the veins, especially the venules, for the pathological physiology of the circulation lies in the fact that if an unusually great proportion of the venules is relaxed or the forces which return blood from the venules to the heart become impaired, a large portion of the total blood volume is pooled in the venules. The consequence is lowering of the pressure in the large veins and diminished venous return to the heart with equal drop in cardiac output and depression of arterial pressure On the other hand, constriction of the venules must lead to displacement of blood into the large veins and resultant increase in the venous return to the heart with acceleration of the circulation

Such variations in the capacity of the venules may result either from changes in the tone of the venules themselves or from the influence of external forces acting on these small vessels Gollwitzer-Meier[23] has shown that increase in the carbon dioxide content of the blood results in contraction of the veins through its action on the vasomotor center, and that this venous contraction is accompanied by acceleration of the circulation Of the extrinsic factors affecting the capacity of the veins, contraction of the skeletal muscles is perhaps the most important. Henderson is of the opinion that the low venous pressure in shock is due largely to decreased tone of

the skeletal muscles which diminishes pressure on the venules and thus increases their capacity, with resultant stagnation of blood within them (page 628). During muscular exercise, the opposite is true; contraction of the skeletal muscles squeezes out the venules and the pressure in the large veins is elevated with resultant increase of the venous return to the heart and speeding up of the circulation. It is a matter of everyday observation that clenching the fist during venepuncture causes the blood to spurt from the needle; this is due to the squeezing out of the veins, the valves directing the blood centrally. Mall[46] long ago observed that the contractions of the intestine similarly squeeze out the intestinal veins.

The Circulating Blood Volume.—Increase or decrease of the circulating blood volume tends to induce parallel changes of the pressure in the peripheral veins in which clinical measurements are carried out. However, this tendency is opposed by a number of compensatory mechanisms at the disposal of the organism, with the result that in health the circulating blood volume and the venous pressure rapidly return to their previous level following the transfusion or venesection of even considerable volumes. Bayliss and Starling[3] found that the marked rise in venous pressure which follows the rapid introduction of 500 cc of physiological salt solution is of but brief duration. Similarly, Meek and Eyster[48] determined in dogs that the increase in diastolic heart size and venous pressure induced by the intravenous injection of acacia saline, physiological saline, or blood in quantities varying from 25 to 103 per cent of the total blood volume is of but limited duration. In humans, Villaret[60] noted no change in venous pressure following the slow intravenous administration of 500 to 1000 cc. of serum or diluted neoarsphenamine. In the observations of Caughey, Richards[11] and their associates the intravenous administration of 1500 cc of physiological saline at a rate of 50 cc. per minute produced little change in the venous pressure of the normal person. Likewise, the removal of comparatively large volumes of blood does not long affect the venous pressure when the circulatory apparatus is healthy. Plumier[52] found that seven minutes after the abstraction of 750 cc. of blood from a dog weighing 30 kg., the venous pressure had returned to its previous level. In man, Eyster and Middleton[18] showed that the removal of 10 per cent of the circulating blood volume has no more than a transitory effect on the venous pressure, the arterial pressure and the cardiac output. Villaret[60] and his collaborators observed no change in venous pressure as a result of venesection of 300 cc. carried out for purpose of transfusion.

Doubtless, a number of mechanisms participate in the maintenance of the approximate constancy of the circulating blood volume and the venous pressure. Perhaps the most rapid of these is the displacement of blood from the rapid circulation into the depots

(spleen, liver, subpapillary plexuses of the skin, etc) or *vice versa*, as the occasion calls for. Another important mechanism is the transudation of fluid from the blood stream into the tissues, or the reverse, which often occurs with remarkable rapidity. Probably, also, the state of contraction of the veins is adapted to the blood volume and thus plays a part in maintaining the venous pressure; following hemorrhage, the superficial veins seem contracted while in patients with polycythemia they often appear dilated Similar observations can often be made in the retina.

Even in instances in which the circulating blood volume is greatly altered by disease, as long as the organs of circulation are functionally efficient they may be able to adapt themselves to the changed blood content and maintain the venous pressure at the usual level. This is often strikingly illustrated in polycythemia vera Thus, in a recent case, despite the prodigious circulating blood volume of 200 cc per kilogram of body weight, the venous pressure was 4 5 cm. of water.

Of course, there are limits of change of blood volume beyond which the compensatory mechanisms no longer succeed in maintaining the venous pressure even though the vascular system was previously normal. This is particularly the case if the change in blood volume transpires very rapidly. Thus following great hemorrhages (*e. g*, in peptic ulcer) it is common for the veins of the upper extremity to be so empty that there is almost no pressure within them and it is necessary to cut down on the vein to perform a transfusion.

In circulatory disease, the regulatory mechanisms often do not function as efficiently as in health, with the result that both circulating blood volume and venous pressure may deviate from the normal The detailed studies of Brandt[7] have shown that, in general, venous pressure and circulating blood volume undergo parallel changes. He found this true in various forms of circulatory insufficiency as well as when the blood volume is altered by the administration of epinephrin and other agents. In insufficiency of the right heart, both blood volume and venous pressure are generally elevated, although there is no close proportionality. Contrary to their observations in health (page 102), Caughey, Richards and their co-workers found that in patients with heart failure the slow intravenous administration of salt solution produces a pronounced elevation of venous pressure. And further in such patients, contrary to what occurs in health, venesection generally produces a marked fall in both circulating blood volume and venous pressure. In right heart failure, venesection of 500 cc is not uncommonly followed by a fall of 10 or even 15 cm in venous pressure In other cases, the drop is but small, but is rarely absent if the initial venous pressure was considerably elevated. Moreover, the depression of

the venous pressure may last a considerable time, or indefinitely if the patient improves. Contrariwise, in peripheral circulatory failure (shock), both circulating blood volume and venous pressure are depressed, and a large blood transfusion may be followed by a marked rise in venous pressure, which is usually not the case in the absence of circulatory failure. Recently, in such a patient, a transfusion of 600 cc resulted in a rise of venous pressure to 6.5 cm. from a pressure so low that it could not be measured by the direct method.

An exception to the general parallelism of venous pressure and circulating blood volume in circulatory failure is encountered in isolated insufficiency of the left heart. In such patients, I have repeatedly observed increase in circulating blood volume despite normal venous pressure, the surplus blood is evidently in the lungs.

Respiration and Other Extravascular Aids to Venous Return.—Because many of the veins are equipped with valves, extravascular forces which compress the veins must aid the propagation of blood toward the heart. The chief mechanisms which function in this manner are the contraction of the skeletal and intestinal muscles and the respiratory movements. The significance of the activity of the skeletal muscle in maintaining the venous pressure has already been considered It was pointed out that the powerful muscular contractions during exercise play an important part in elevating venous pressure; indeed, there are observations in which muscular contraction caused the pressure in individual veins to exceed the arterial tension.

Respiration and the Venous Return.—The influence of respiratory activity in maintaining the pressure in the veins and favoring the venous return to the heart is very considerable In fact, Eppinger[16] and his associates estimate that between 6 and 25 per cent of the total volume of circulation is to be attributed to the activity of the "respiratory pump." The significance of respiration for the venous flow is shown by the pronounced fall in venous pressure induced by hyperventilation (Bedford and Wright,[5] Henderson, Prince and Haggard[28]) and the rise that occurs during the apneic phase of Cheyne-Stokes breathing (Meyer and Middleton[49]) or prolonged holding the breath.

The respiratory movements aid the circulation mechanically through favoring the venous return to the right heart, and perhaps also by facilitating blood flow through the lungs, although the significance of the latter factor is still doubtful. (See page 537.) It is also possible that variations in the carbon dioxide and hydrogen-ion contents of the blood due to changes in respiration affect the venous flow and pressure.

Significance of the Intrathoracic Pressure for Venous Flow.—The venous return to the right heart is aided by the negative pressure

prevailing within the thorax as a result of the elastic pull of the lungs on the chest wall and mediastinum. The negative pressure is greater during inspiration and less during expiration, averaging about −6 cm of water. Because of this negative intrathoracic pressure, the "effective pressure," as Henderson termed the filling pressure with which the right auricle is distended during diastole, is higher than the pressure in the great veins referred to atmospheric pressure Obviously, the effective pressure equals the difference between the pressure at the mouths of the venæ cavæ and the pressure exerted by the lungs on the outside of the right auricle, both pressures being referred to atmospheric pressure. So that if the pressure in the venæ cavæ averages 1 cm. of water referred to atmospheric pressure (*i e.*, as ordinarily measured with a manometer) while there is a negative intrathoracic pressure of −6 cm. of water, the effective pressure of the blood entering the right auricle is 7 cm. of water Actually, the pressure in the great veins is generally close to zero and may even be negative, but the greater negativity of the intrathoracic pressure results in an effective pressure being exerted, so that the heart is filled

From the all-important point of view of the filling of the heart, the significant venous pressure is not that referred to atmospheric pressure which we measure, but the effective pressure as just defined, *i. e.*, the pressure in the veins referred to that existing in the thorax as a base If the intrathoracic pressure is elevated, it is obviously essential that the venous pressure be correspondingly augmented in order that the effective venous pressure and consequently the filling of the heart be maintained Kroetz[35] found that when he increased the intrathoracic pressure (*i e*, diminished the negative pressure) by introducing air into the pleural cavity, the venous pressure measured in the arm rose exactly as much as the intrathoracic pressure ascended When the intrathoracic pressure is elevated by forced expiration with closed glottis (Valsalva experiment) the venous pressure mounts to great heights On the other hand, depression of the intrathoracic pressure by forced inspiration with closed glottis (Mueller experiment) results in fall in venous pressure. Similarly, Kroetz observed low venous pressure as a result of depressed mean intrathoracic tension due to extensive pleural adhesions which increased the inspiratory traction on the lungs Increased intrapleural pressure in emphysema, due to the diminution in the elastic traction of the lungs, may result in high venous pressure in the absence of heart failure (page 535). Elevation of intrapleural pressure also plays a part in the genesis of the augmented venous pressure that may result from extensive accumulation of fluid or air in the pleura; but other factors, notably displacement of the mediastinum with kinking of the veins and direct pressure of the fluid or air on the superior vena cava are

generally more significant. It is important to bear in mind that increase in venous pressure can be due to these mechanical extravascular factors and does not necessarily imply myocardial weakness

Influence of Respiratory Phases on Venous Return—The consequences of the alternation of inspiration and expiration for the venous flow are complex and not entirely understood; they are affected by whether the breathing is predominantly costal or diaphragmatic According to Krogh and Lindhard,[25] the costal type of breathing tends to increase cardiac output, while respiration of abdominal type lowers the minute volume; this difference is in all probability largely the consequence of corresponding alterations in venous return to the heart. The decreased intrathoracic pressure during inspiration favors the venous return from the superior vena cava through augmented thoracic aspiration, so that with each inspiration a wave of negative pressure travels peripherally along the veins of the upper extremity (Burton-Opitz[9]). The thoracic aspiration during inspiration also affects the inferior vena cava, but here the effects of greater intra-abdominal tension due to the descent of the diaphragm appear to be quantitatively more important The inspiratory descent of the diaphragm increases intra-abdominal tension, which serves to squeeze blood out of the liver and portal tributaries into the inferior vena cava and thus augments the venous return (See page 65.) On the other hand, the compression of the inferior vena cava by the greater intra-abdominal tension hinders the venous return from the lower extremities during inspiration. In man, though perhaps not in all experimental animals, this factor appears to be more significant than the transmission of the greater thoracic aspiration during inspiration. The result is that in humans—as Mosso long ago showed by his ingenious balance method (page 175)—the venous return from the lower extremities is impeded during inspiration, and blood accumulates there during this phase of respiration.

The usual effect of inspiration is thus to increase the venous return from the superior vena cava and portal vein but to diminish that from the lower extremities. Since the volume of blood emanating from the superior vena cava and portal vein together* is, at least under most conditions, greater than that from the lower extremities, it would seem that the venous return to the heart must generally be greater during inspiration.

Another way in which the respiratory movements affect the circulation is through inspiratory dilatation of the heart, especially the thin-walled auricles, as a result of the lowering of intrathoracic

* According to the investigations of Grab, Janssen and Rein[23] with the Thermostromuhr, between 50 and 73 per cent of the total return from the inferior vena cava comes from the portal vein Of course, this proportion must vary greatly with digestive and other activities, and is doubtless also altered under pathological conditions

pressure. The consequent increased filling of the heart during inspiration induces, in accord with Starling's law of the heart, a more powerful systole.

Respiratory Undulations in Venous Pressure.—Despite these various effects of respiration on the venous flow, respiratory fluctuations in venous pressure are generally not appreciable when the measurement is carried out by the common clinical methods on a subject who is breathing as usual. The reason for this is that the undulations are damped by the great inertia of the blood column from the heart to the antecubital vein plus that of the manometric system. If very sensitive apparatus is used, the respiratory variations in pressure in the antecubital vein can be graphically recorded. (See Kendrew.[33]) Using the Moritz-Tabora method (page 113) and fine needles, Kroetz[55] did not observe respiratory undulations, while with needles of 0 8 mm. bore, the maximum respiratory excursions were 0.4 cm. of water, being generally under 0.2 cm. He found that even respiration of maximum depth in muscular men did not occasion respiratory excursions in venous pressure of more than 0 8 cm. Kroetz observed well-marked respiratory excursions in venous pressure (up to 2 5 cm.) only in individuals with a rigid thorax, either with extensive pleural adhesions or with tenacious exudate in the bronchi—conditions which occasion abnormally great variations in intrathoracic pressure during each respiratory cycle Similar observations of well-marked respiratory variations in venous pressure were made by Buerger[8] in emphysema and bronchial asthma. The changes in venous pressure during Cheyne-Stokes breathing have already been mentioned

The Activity of the Heart.—The output of the heart is largely determined by the diastolic filling, which is in turn dependent on venous pressure If venous pressure is elevated, the greater diastolic filling of the heart results in increased systolic discharge, the effect of which is to deplete the veins more thoroughly and thus tend to lower venous pressure The reflex acceleration of the heart by increased pressure within the veins and heart (Bainbridge reflex) works in the same direction The result is that *within quite wide limits of venous return the functionally competent heart maintains the venous pressure at a constant level*

On the other hand, decrease in the output of the right ventricle entails accumulation of blood in the systemic veins and tendency to increased venous pressure This is well illustrated by the effects of vagus stimulation in the experimental animal, in which the slowing and decreased output of the heart are accompanied by fall in arterial and rise in venous pressure. That decrease in the output of the human heart due to disease likewise causes rise in venous pressure will be discussed in the next section. In fact, there is every reason to believe that in the evolution of right heart failure,

increase in systemic venous pressure may precede diminution in the output of the right ventricle. For higher venous pressure entails greater diastolic filling of the right ventricle and, according to Starling's law of the heart, a more powerful systole of the chamber, so that its output may be maintained despite the functional impairment

It has long been known that even in health the increased venous return during vigorous exercise elevates venous pressure, and Tetelbaum[58] and his associates have found that in heart failure, as would be anticipated, this rise is greater and more protracted.

CLINICAL SIGNIFICANCE OF THE VENOUS PRESSURE

Figuratively speaking, the systemic veins may be regarded as a reservoir which is filled from the periphery and emptied by the cardiac pump The venous pressure affords a measure of the filling of the reservoir at which the supply of blood from the capillaries and the removal of blood by the right heart are in dynamic equilibrium. If the peripheral vessels allow little blood to pass into the large veins, the level of the reservoir and with it the venous pressure is low, while if the right heart is insufficient the reservoir fills and the venous pressure rises.

Accordingly, apart from mechanical mediastinal obstruction, *elevation of the venous pressure above the normal bespeaks heart failure, while peripheral failure tends to lower the venous pressure.*

Determination of the venous pressure thus often enables the physician to determine whether circulatory failure is due to cardiac weakness or is primarily the result of peripheral circulatory failure. There are many instances of circulatory failure—notably in pneumonia and other acute infections especially when they occur in individuals with pre-existent heart disease, in hypertension with cerebral accident, and in arteriosclerotic diabetics with severe acidosis—in which the estimation of the venous pressure is of great or even indispensable aid in deciding whether the circulatory derangement is of cardiac or of peripheral origin, a decision momentous for the therapeutic procedure to be adopted.

It is to be borne in mind that both cardiac and peripheral factors may be coincidently concerned in the pathogenesis of circulatory failure, and then tend to neutralize the effects of one another on the venous pressure. This is seen, for example, in infections, in which there may be damage to the myocardium and coincident injury to the peripheral vessels or operation of other mechanisms (*e. g.*, vomiting) tending to lower the blood volume

Other important clinical applications of the measurement of the venous pressure are: (1) The decision whether enlargement of the liver, ascites or edema of the lower extremities are due to right

heart failure, or such conditions as cirrhosis of the liver, intra-abdominal neoplasm, or renal disease, which are not accompanied by rise in venous pressure; (2) the differentiation whether cyanosis and dyspnea are due to pulmonary lesions or to right heart failure; and (3) following the course of right heart failure.

Failure of the Right Heart.—Insufficiency of the right side of the heart is the cause *par excellence* of elevated venous pressure; so much so that a pronounced rise in venous pressure—to over 15 cm. by the direct method—is almost pathognomonic of overstrain of the right heart The only other causes of such elevation in venous pressure are hypodiastolic failure of the heart and mechanical compression of the great veins by mediastinal masses. High venous pressure may develop in any of the diseases in which the right heart gives way, whether this be primary, as in pulmonary or tricuspid disease, or secondary to failure of the left ventricle in aortic, mitral or hypertensive disease In all such cases with elevated venous pressure, the evidence of the failure of the right heart is afforded at necropsy by the finding of dilatation of the right ventricle and auricle.

The venous pressure may rise to great heights in right heart failure; figures of over 20 cm are common, 30 cm is not rare, and over 40 cm has been observed The elevation may occur very rapidly. I have seen the venous pressure rise in a patient with arteriosclerotic heart disease from 7 5 cm. in the morning to 24 cm. in the middle of the afternoon Remarkably enough, however, in extreme and generally terminal stages of right heart failure, the venous pressure may fall—apparently as a result of vasoconstriction in the extremities evoked by the great diminution in cardiac output. (See page 527.)

It is to be emphasized that definite elevation of venous pressure above the upper limit of normal is not generally an early sign of insufficiency of the right heart and may not be demonstrable at any time in the lesser degrees Thus, in patients with mitral disease it is not rare to encounter a venous pressure of less than 8 cm. although the enlargement of the liver and dependent edema testify to the presence of insufficiency of the right side of the heart One reason why the venous pressure reading does not constitute a sensitive index of the lesser degrees of right heart failure is our inability to determine accurately the level of the right auricle, which forms the zero point for the reading; the result is that, especially in deep-chested individuals, a measurement which seems within the limits of normal is actually abnormally high in relation to the right auricle (see page 114), as shown by the lower level after the patient has improved. Another reason why the venous pressure reading may not unequivocally disclose the lesser grades of right heart failure is a consequence of the fact that in health the veins are not com-

pletely filled with blood so that many of them are partly collapsed The initial accumulation of blood in the veins as a result of right heart failure is accommodated by filling out the collapsed veins During this stage, there is little rise in pressure. Only after the veins are filled does further accumulation of blood rapidly manifest itself by rise in pressure because of the comparative inelasticity of the venous wall. At this stage, a comparatively small increment in the blood content of the veins may result in marked rise in pressure. Conversely, the removal of so small an amount of blood as 300 cc by venesection in such patients may depress the venous pressure by 10 cm. Moreover, when the veins are considerably dilated by the increased pressure within them, it seems probable that the valves may become functionally insufficient, so that the central rise in pressure is better transmitted to the peripheral veins. The marked enlargement of the mouths of the hepatic veins often illustrates strikingly how marked the dilatation of the veins in right heart failure may be. In such cases as Moschcowitz[61] has pointed out, phlebosclerosis may develop, doubtless as a result of the increased venous pressure.

Moreover, as already indicated (page 100), accumulation of blood in the liver and portal tributaries in right heart failure may also militate against elevation of peripheral venous pressure. The enlargement of the liver may precede the rise in venous pressure, and it is also common for the hepatic swelling to persist for a long time after the venous pressure has returned to normal. The mechanism of the enlargement of the liver under these circumstances is further discussed in Chapter XV.

In those cases of relatively slight insufficiency of the right heart in which the antecubital venous pressure is within the limits of normal, the right-sided insufficiency can often be demonstrated by the engorgement of the jugular veins and rise in antecubital venous pressure that follows compression of the abdomen (page 256).

It would seem probable that the increased venous pressure in right heart failure, deleterious though it is in so many ways, also serves a compensatory function. For the higher venous pressure augments the diastolic filling of the heart and this, according to Starling's law of the heart, increases the energy of systole. Through the Bainbridge reflex (page 295), the increased venous pressure also tends to accelerate the heart. Both these mechanisms increase the effectiveness of the hypodynamic right heart in maintaining the circulation.

Left Heart Failure.—In typical instances of isolated left heart failure, the venous pressure is within normal limits Patients with this circulatory syndrome resulting from aortic or mitral valvular disease, hypertension, coronary arteriosclerosis, or other conditions may have a venous pressure of under 8 cm. of water for long periods

of time, even several years, despite the presence of dyspnea on exertion, paroxysms of cardiac asthma, and physical signs of intense pulmonary engorgement The venous pressure in left heart failure is discussed in more detail in Chapter XXIV.

Hypodiastolic Failure.—Increase in systemic venous pressure is often a striking manifestation of hypodiastolic failure, whether it be due to mechanical incarceration of the heart by pericardial effusion or adhesive mediastino-pericarditis, or to shortening of diastole in excessive tachycardia Further details are given in Chapter XXX.

Peripheral Circulatory Failure.—In shock, the systemic venous pressure is characteristically depressed (Chapter XXXI)

Regional Differences in Venous Pressure.—Burwell[10] and his associates have found the venous pressure of the same order of magnitude in the arm and the leg in both health and individuals with high venous pressure due to heart failure On the other hand, they and other observers have shown that when intra-abdominal pressure is increased by pregnancy or such pathological causes as tumors or the ascites of cirrhosis of the liver, the femoral venous pressure may be far higher than that in the antecubital veins. Similarly, mediastinal tumors or aneurysm may produce a higher venous pressure in one arm than in the other or elevate the antecubital above the femoral venous pressure. Hussey[32] found the venous pressure significantly different in the two arms in 85 per cent of patients with aneurysm of the aorta or innominate artery.

The pressure in the antecubital and external jugular veins is about the same in both health and the large majority of patients with elevated venous pressure due to heart failure But in individuals with the clinical picture of shock due to sudden onset or intensification of severe heart failure, the pressure measured by the ascending L-tube method (page 113) in the antecubital veins may be much lower than in the veins of the neck, this is presumably a manifestation of vasoconstriction in the extremities called forth by extreme diminution in cardiac output (see page 631)

THE CLINICAL MEASUREMENT OF VENOUS PRESSURE

Three general methods are in use for the clinical measurement of venous pressure: (1) Non-instrumental observation, (2) indirect methods; (3) direct methods

Non-instrumental Methods.—Gaertner[20] long ago recommended the following simple procedure for the estimation of the venous pressure. The patient is comfortably seated, if in bed, he is propped up on pillows The arm is allowed to hang down until the veins on the back of the hand are well filled. Then the observer lifts the completely relaxed upper extremity until the vein selected for observation (usually on the back of the hand) collapses. The

height above the upper border of the fifth rib, which is taken as the level of the right auricle, at which the vein collapses indicates the venous pressure The normal values range between 4 and 10 cm. There are many subjects, especially obese women and children, in whom the veins are not sufficiently prominent to render the method feasible The same is true in some elderly laborers with sclerotic and thickened veins. Very often, the height at which the veins collapse is indefinite. Even when the level at which the vein collapses seems quite definite, one is often surprised at the discrepancies with the direct method. Nevertheless, the method is frequently of value for rough orientation concerning the venous pressure.

Lewis[39] has described another non-instrumental method for the approximate evaluation of the venous pressure. It is based on the observation of the height to which the blood rises in the external jugular vein, which may be regarded as a manometer extending into the right auricle In health, the upper level of the blood column in the external jugular vein is in the horizontal plane passing through the upper end of the manubrium. When the patient is reclining flat, this plane corresponds to about the junction of the upper and middle thirds of the neck When the venous pressure is elevated, the filling of the external jugular vein extends higher, and the elevation of venous pressure may be estimated by measuring the *vertical* distance between the upper end of the blood column in the external jugular vein and the top of the sternum. If the venous pressure is very high, it is necessary that the patient be seated in order that the upper end of the blood column can be seen. Inspection of the cervical veins often enables the recognition of increased venous pressure at a single glance, an observation that clinicians have been making for generations The method of Lewis often gives a valuable approximation of the venous pressure, and is to be recommended for preliminary orientation in the study of all cases of circulatory disease. However, there are many individuals in whom the anatomical disposition of the veins of the neck or obesity render the observation of the cervical veins difficult or impossible. In some cases, it has seemed to me that contraction of the veins rendered them invisible, for at other times they could be seen readily. Here, again, one is often surprised by discrepancies with the direct method of measuring venous pressure.

Indirect Methods.—These depend on the measurement of the external pressure necessary to compress a superficial vein. The methods in use at present utilize a pneumatic chamber connected with an inflation bulb for increasing the pressure and a manometer for measuring it. There is a transparent window for observing the pressure at which the vein collapses The apparatus of this type most used in this country was devised by Eyster,[17] another has more recently been described by Landis[37] and his associates Using his apparatus, Eyster found that under basal conditions the venous pressure in healthy individuals is usually between 4 and 6 cm.

of water The highest pressure observed in hundreds of such persons was 11 cm, which he regards as the upper limit of normal

Though it is now a good many years since the indirect methods of determining venous pressure were introduced, their use has never become widespread in clinical medicine It would seem that considerable practice is required before one becomes adept in judging the pressure at which the vein is collapsed In obese individuals or those with small superficial veins, especially women, the point of collapse of the vein is difficult or impossible to determine Moreover, the presence of phlebosclerosis, which is common in elderly individuals who have done hard manual work, introduces an error due to the pressure required to overcome the rigidity of the venous wall A similar error may result from hypertonus of the venous wall, which is probably not uncommon in heart failure The quantitative significance of such errors due to the venous wall remains to be determined, but it would seem that in comparison to the low intravenous tension they may be considerable

Direct Methods.—In the direct methods a needle is inserted into the lumen of a superficial vein and connected to a manometer.

The direct method was first introduced into clinical medicine by Moritz and Tabora[60] Their manometric system consists of a glass tube connected to an intravenous needle by rubber tubing and an adapter The entire apparatus must be sterile. The system is filled with sterile physiological salt solution and the needle is inserted into one of the antecubital veins The fluid runs into the vein until the hydrostatic pressure of the fluid column in the tube equals the venous pressure The vertical distance in centimeters between the top of the fluid column in the manometer and a horizontal plane passing through the right auricle is the venous pressure in centimeters of water. According to Moritz and Tabora, the level of the right auricle in the recumbent position is 5 cm. beneath the anterior surface of the chest at the insertion of the fourth rib. By this method, Moritz and Tabora found that the normal venous pressure ranges between 1 and 9 cm of water; the vast majority of the readings are between 4 and 8 cm A convenient modification of Moritz and Tabora's method has been described by Griffith, Chamberlain and Kitchell,[25a] who use a side arm syringe.

Villaret[60] has substituted an aneroid manometer for the water manometer.

Taylor, Thomas and Schleiter[57] have greatly simplified the direct method for determining the venous pressure. I have used their method with slight modifications since it was published and have found it satisfactory The great advantage of the method is its extreme simplicity. The apparatus consists of an L-tube of 4 mm. bore, the tip of the short limb being ground to fit an intravenous needle, while the long limb is graduated in centimeters. The completely relaxed upper extremity of the reclining patient is supported on a pillow so that the flexor surface of the bend of the elbow is at the level of the caval openings in the right auricle, *i. e*, 5 cm.

beneath the anterior chest wall at the insertion of the fourth rib. The importance of complete muscular relaxation of the extremity is worthy of reiteration. The needle and manometric tube are sterilized. It is well to run a little sterile anticoagulant (10 per cent sodium citrate) solution through the tube and needle just before use. The skin is prepared for venepuncture A blood pressure cuff is inflated around the arm to about 40 mm. of mercury. The needle is attached to the manometer and inserted well into the vein As soon as blood enters the tube, the cuff is released. The tube is held vertically and the blood is allowed to mount until it reaches a stationary level. After noting this level, it is well to compress the arm, which causes a further rise in the blood column and thus verifies the patency of the system. A further check can be obtained by allowing the blood to flow back into the vein and noting the level at which it becomes stationary.

If desired, and as a further check, the tube can be used for the Moritz-Tabora method by filling it with sterile physiological salt or sodium citrate solution and allowing the fluid to run into the vein until stopped by the venous pressure, the height of the fluid column then gives the venous pressure.

I have found the method of Taylor, Thomas and Schleiter adequate for general clinical use. It combines the theoretical advantages of the direct method with extreme simplicity; the apparatus can be readily fashioned at negligible expense.

Normal Values of the Venous Pressure by the Direct Method.—Using the L-tube method, and a zero point 5 cm posterior to the tourth costochondral junction, the normal venous pressure is less fhan 10 cm. of water In the large majority of individuals the pressure is between 3 and 8 cm However, it is not rare in healthy persons to obtain readings of only 1 or 2 cm As pointed out by Lyons, Kennedy and Burwell,[44] this occurs especially in deep-chested individuals. These investigators find that with a large antero-posterior diameter of the chest, the posterior surface of the right auricle actually lies more posterior than 5 cm. dorsal to the fourth costochrondal junction, so that the use of this zero point results in underestimation of the true venous pressure when compared to that of less deep-chested persons. Their findings indicate that the posterior surface of the right auricle is more closely related to the posterior than to the anterior surface of the chest wall. They suggest that in adults the zero point be taken as 10 cm. anterior to the skin of the back With this point of reference and the Moritz-Tabora method, Burwell and his pupils find the normal venous pressure between 5 and 15 cm. of water. For a splendid discussion of the direct measurement of venous pressure, the reader is referred to the paper of Lyons, Kennedy and Burwell.[44]

THE VENOUS PULSE

Pulsations can be seen in the cervical veins of most healthy individuals; according to Hewlett,[30] in over 80 per cent. In the large veins of the extremities, visible pulsation does not occur in health. The venous pulse can be studied either by simple inspection of the cervical veins or by graphic records (phlebograms) taken with a receiver over the pulsating vein It was through the interpretation of such graphic records that the fundamentals of our knowledge of the cardiac arrhythmias were unveiled in the classic researches of Mackenzie[46] and Wenckebach[61] For a time, the phlebogram was extensively used in practical clinical work. Unfortunately, to obtain a good tracing of the venous pulse is often a task of considerable difficulty, and the interpretation of the records is frequently obscure. The electrocardiogram has proved, in general, infinitely superior to mechanical tracings for the study of the rhythm of the heart, and the latter are now scarcely used for other than investigative purposes For this reason, the present section will be confined to a few brief, general remarks on the venous pulse, and the reader referred for details to the above-mentioned works They are well worth study, if only as examples of how much information can be obtained from a simple technic used with high intelligence. For the correlations with electrocardiography, the reader is referred to the monumental treatise of Lewis[41]

The Normal Phlebogram.—The pulse in the cervical veins mirrors the pressure changes in the right auricle. Because of the free communication with the veins of the neck, any change in the pressure in the right auricle quickly is reflected in a corresponding retardation or acceleration of the flow in these veins When the pressure in the right auricle rises, the flow in the veins is retarded and they swell, while a fall in intra-auricular pressure is accompanied by collapse of the veins as they empty into the auricle. As a result of the changes in intra-auricular pressure, three main positive waves and two prominent negative depressions are present in the phlebogram of each cardiac cycle These, with the letters applied to them by Mackenzie and now universally used, are as follows:

1. A wave due to auricular systole (*a* wave)
2. From the descending limb of the *a* wave, there springs a wave which marks the onset of ventricular systole (*c* wave). Mackenzie believed that the *c* wave is due to the transmission of the pulsation from the neighboring carotid artery to the jugular vein, but this has been contradicted by Hirschfelder,[31] Bard,[1] and others. According to Hirschfelder, it is due in part to the pushing-up of the tricuspid valves at the onset of ventricular systole and in part to the emptying of the coronary veins into the right auricle.

The *c* wave is followed by a depression (*x* depression). This depression occurs at the time the auricle is relaxing, but Hirschfelder enumerates other factors which he believes are also concerned in its causation. The *x* depression is followed by

3. A broad wave (*v* wave) due to the diastolic filling of the auricle The apex of the *v* wave indicates the time (or slightly after the time) when the tricuspid valves open.

The *v* wave is followed by a depression (*v* depression) as the blood flows from the auricle into the ventricle. The depression rises slowly as blood flows into the auricle from the veins until the next cycle is started by auricular systole

Various inconstant and usually minute waves have been described. Of these, the most important is the *h* wave of Hirschfelder, independently observed by Hirschfelder and Gibson,[21] which follows the *v* wave and is ascribed by these investigators to the floating together of the tricuspid curtains This apparently occurs at that time of ventricular diastole which marks the end of rapid ventricular filling and the onset of Henderson's period of diastasis For the relations of the *h* wave to the third sound of the heart and protodiastolic gallop rhythm, see page 391.

Inspection of the Cervical Veins.—This is usually best accomplished on the right side of the neck with the head so turned as to relax the sterno-cleido-mastoid muscle. The position of the patient and the height in the neck at which the amplitude of the pulsations is greatest is largely determined by the venous pressure. The amplitude of movement of the vein is greatest where the venous pressure most closely approximates the atmospheric pressure. With normal or but moderately elevated venous pressure, the pulsations are generally of greatest amplitude and most readily observed over the jugular bulb in the root of the neck with the patient supine. On the other hand, if the venous pressure is very high, there may be no pulsation visible in the reclining posture and the patient should be gradually sat up until the position is reached in which the pulsations are best seen. Generally, the pulsations are most ample at the top of the blood column in the veins.

Pulsation in the veins of the neck is usually easy to differentiate from the beating of the carotid. The error usually made is to mistake venous pulsation for arterial, the reverse mistake is rare. Pulsation just above the clavicle, over the jugular bulb, is generally venous. When a pulsation higher in the neck is venous, other evidences of venous engorgement are usually manifest When there is more than one pulsation for each cardiac cycle, it is, of course, venous The carotid pulsation, if visible, is also palpable, the venous only rarely so and then is accompanied by other evidences of pronounced systemic venous engorgement. Actually, carotid pulsation is rarely prominent apart from florid aortic regurgitation,

Graves' disease, severe anemia, extreme emaciation, pronounced arteriosclerosis, cardiac overactivity of nervous origin, aneurysm, and heart block; in the last, one may discern frequent venous pulses corresponding to the auricular systoles.

Despite the three waves which the phlebogram contains, inspection of the cervical veins in health generally reveals but two waves. This is evidently because the *a* and *c* waves are fused in one undulation, which is followed by the *b* wave. Furthermore, under normal circumstances the systolic collapse of the vein is more striking than the swelling, for which reason the normal venous pulse is often called the *negative* venous pulse Because of the presence of the auricular wave, it is sometimes also called the *auricular* form of the venous pulse.

Perhaps the most important information that the clinician derives from inspection of the cervical veins is that regarding the height of the venous pressure (page 112). Much can also be learned concerning the arrhythmias by the naked-eye study of the venous pulse, but for details regarding this the reader is referred to the above-mentioned works. Here may be mentioned the frequency with which auricular flutter and heart block can be detected by observation of a higher frequency of the venous pulse than of the apex beat. On the other hand, Prinzmetal and Kellog[55] found that some cases of ventricular tachycardia can be recognized by an apical rate faster than the jugular pulsations.

The Ventricular Form of the Venous Pulse.—It was mentioned above that in the normal (auricular or negative) form of the venous pulse, there are two waves, each followed by a depression, and the most striking event is the systolic collapse of the vein In the ventricular form of the venous pulse, on the contrary, only one wave is seen, and this consists in a sustained systolic filling of the vein, which collapses in diastole

The condition in which the ventricular form of the venous pulse most often appears is auricular fibrillation The mechanism of its production is as follows: Because of the uncoordinated contraction of the auricles, the *a* wave is, of course, absent. Furthermore, instead of being almost empty at the beginning of ventricular systole, as is normally the case, the auricle is already distended with residual blood. The result is that the blood flowing into the auricle from the great veins meets with resistance, the pressure within the veins rises, and they are distended. So to speak, there is anticipation of the normal *v* wave. Under normal circumstances, with the auricle practically empty at the beginning of ventricular systole, as a result of its own contraction, the blood flowing in from the venæ cavæ must first distend the chamber somewhat before the resistance it meets is sufficient to be marked by a positive wave, the *v* wave, in the cervical veins, and there is thus a distinct

interval between the *c* wave at the beginning of ventricular systole and the *v* wave But when the auricle is already distended, the effect of the blood flowing in from the great veins manifests itself immediately and the *v* wave merges with the *c* wave to constitute one large positive wave during ventricular systole. Of course, if there is tricuspid insufficiency, the regurgitated blood adds itself to that returning from the veins and the single positive systolic wave is all the more pronounced But it is to be emphasized that the ventricular form of the venous pulse is not necessarily a sign of tricuspid insufficiency; it merely indicates that the auricle has not emptied.

The type of venous pulse in tricuspid stenosis is mentioned on page 550

Pulsations in the Veins of the Extremities.—It was mentioned above that in health no pulsations are visible in the veins of the extremities. In severe right heart failure with systemic venous engorgement, on the other hand, pulsations may be visible in the large superficial veins of the upper extremity, especially the antecubital veins The frequency with which such pulsation is to be detected in severe right heart failure was brought out in the excellent paper of Kerr and Warren,[34] to which the reader is referred. They observed 56 patients with peripheral venous pulsations, mostly within a period of eight months Careful observation with the arm raised to various levels is usually necessary to detect the phenomenon. Peripheral venous pulsation is a sign of severe right heart failure, and Kerr and Warren found that it is of serious prognostic significance. In very rare instances of aortic regurgitation, transmitted pulsation is visible in the veins.

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CHAPTER VII

EXERTIONAL DYSPNEA

DYSPNEA* is the symptom *par excellence* of a failing heart. It occurs in varying severity in cardiac failure of all types and is most often the first subjective token that the heart is embarrassed in maintaining the circulation in accord with the dictates of the metabolism of the moment. Three varieties of dyspnea result from circulatory failure:

1. *Exertional dyspnea,* in which the shortness of breath is called forth or accentuated when the work of the heart is augmented, usually through not solely, by physical exertion or emotion. In severe, exetional dyspnea, the demands on the heart embarrass it under basal conditions and the patient is short of breath even at complete rest Exertional dyspnea is much the most common form of cardiac dyspnea. It is sometimes called continuous dyspnea, to differentiate it from the following forms.

2 *Paroxysmal dyspnea,* or *cardiac asthma,* in which the shortness of breath occurs in paroxysms, not motivated by obvious physical exertion or emotion.

3. *Periodic (Cheyne-Stokes) dyspnea* occurs in Cheyne-Stokes breathing, in which the hyperneic phase is sometimes accompanied by the subjective sensation of dyspnea

In all these forms of dyspnea, the shortness of breath may be aggravated in the recumbent posture and alleviated by elevation of the upper part of the body—*orthopnea.*

PATHOGENESIS OF EXERTIONAL DYSPNEA

Historical and Introductory.—The conceptions of the pathogenesis of cardiac dyspnea held by the first students of the subject were surprisingly similar to those in the ascendant today When Vieussens[56] described mitral stenosis over two centuries ago, he attributed the breathlessness to interference with the free entry of air by engorgement of the lungs with blood Corvisart[9] followed a similar line of thought, believing that in many instances cardiac dyspnea "is due solely to the accumulation of blood in the vascular system of the lung" These keen clinicians had thus discerned what appears today to be the most important single factor in the pathogenesis of cardiac dyspnea.

* "Dyspnea is the consciousness of the necessity for increased respiratory effort" (Meakins) The most important recent investigations on cardiac dyspnea are those of Harrison and his pupils, which are summarized in his monograph[22] An excellent survey of dyspnea in general has been published by Christie[7]

Subsequent theories of the genesis of breathlessness in heart disease have been corollaries of the dominant physiological doctrines of the regulation of respiration in health. As oxygen want and carbon dioxide excess waxed and waned in the esteem of physiologists searching for the chemical excitant of the respiratory center, their counterparts flourished as theories of dyspnea Later, when it was thought that the hydrogen-ion concentration of the blood governs respiration, attempts were made to explain cardiac dyspnea on the basis of changes in the acid-base equilibrium of the blood And when Gesell[20] collected strong evidence that alterations in the composition of the blood affect respiration through the intermediacy of the hydrogen-ion concentration in the tissues of the respiratory center, more attention was paid to the rôle of the circulation through the central nervous system in the production of cardiac dyspnea.

Adequate appreciation of the significance of changes in the mechanics of pulmonary ventilation in the pathogenesis of cardiac dyspnea is comparatively recent, and largely due to the investigations of Peabody[19] and his pupils Also very important have been the recent studies of Harrison[22] and his associates, which have revealed the inadequacy of "chemical" explanations of many instances of cardiac dyspnea, and have directed attention to the rôle of nervous reflexes, especially those initiated in the engorged lungs The newer discoveries of the reflex control of respiration *via* the afferent nerves from the carotid sinus and aorta have as yet hardly been evaluated in their relation to dyspnea

We shall consider the mechanisms involved in the pathogenesis of exertional dyspnea in the following overlapping categories·

1. Pulmonary factors
2. Changes in the chemical composition of the blood.
3. Diminution of cardiac output and of blood flow through the respiratory center.
4. Nervous factors.

Finally, the integration of the individual factors tending to produce dyspnea will be discussed.

Pulmonary Factors in Exertional Dyspnea.—We have seen that even two centuries ago the significance of pulmonary engorgement in the causation of cardiac dyspnea was realized Actually, the parallelism between the degree of pulmonary engorgement in heart disease and the severity of dyspnea is often so striking that it can hardly escape the observant clinician In accord with clinical impressions, recent quantitative investigations of the respiratory volumes have shown that passive congestion of the lungs greatly hampers pulmonary ventilation, and that this impairment of ventilation is the fundamental cause of exertional dyspnea in heart disease We shall first describe the mechanisms through which

engorgement of the lungs hampers external respiration, and then turn to the clinical manifestations of the impairment of ventilation and their relation to dyspnea.

The Mechanisms Through Which Pulmonary Engorgement Affects External Respiration.—1 *Diminution in the Capacity of the Alveolar Spaces.*—Traube[54] long ago believed that the cause of cardiac dyspnea is encroachment on the lumens of the alveoli by dilated capillaries in their walls, thus diminishing the volume of air available for gas exchange. Histological examination of the lungs of patients who succumb to heart failure does indeed show that the air spaces are compromised Ectatic capillaries play a part in this process, but thickening of the interstices of the interalveolar septa in long-standing brown induration is also concerned. Transudation of fluid into the air spaces is doubtless of much importance in many cases It seems probable that there may be considerable transudation without manifest auscultatory signs of pulmonary edema The roentgen finding of opaque pulmonary fields affords graphic evidence of the diminished air content of the lungs in many instances of cardiac failure Often, hydrothorax, ascites, meteorism, or enlargement of the liver compress considerable volumes of lung Especially in children, great enlargement of the heart may compromise a notable portion of the pulmonary parenchyma. During the episodes of pulmonary infarction or bronchopneumonia which so often complicate passive congestion of the lungs, dyspnea is usually intensified.

Experimental evidence that engorgement of the pulmonary vessels entails encroachment on the alveolar lumens has been adduced by Romanoff[47] and by Drinker, Peabody and Blumgart.[14] The latter investigators found that when the pulmonary veins are narrowed, entrance of air into the lungs is hampered.

2. *Rigidity of the Lung.*—It is obvious that diminution in the elasticity of the lungs must interfere seriously with the respiratory movements, for expiration is normally effected by the elastic recoil of the lungs and chest wall. Decreased pulmonary elasticity also augments the work of inspiration The first to appreciate the significance of decreased elasticity of the lung in the pathogenesis of cardiac dyspnea was von Basch[37] in his theory of *Lungenstarre* (pulmonary rigidity). The conception of von Basch was that pulmonary engorgement diminishes the elasticity of the lung, which is, so to speak, erected by the increased filling of the vessels Like the fire hose through which water is pumped under high pressure, the pulmonary vessels become more rigid as engorgement raises the intravascular tension. The result is diminished elasticity of the lung. In long standing cases with brown induration of the lung, the extensive fibrosis and frequent edema of the interalveolar septa doubtless also contribute to the loss of elasticity. The less-

ened elasticity of the lung predisposes to dyspnea through curtailing the amplitude and increasing the work of the respiratory movements. The decreased respiratory excursion of the engorged lung is generally demonstrable under the fluoroscope. Pulmonary rigidity is also a primary cause of the decreased vital capacity and increased residual air of the engorged lung

3. *Uneven Ventilation.*—Siebeck[31] believes that in cardiac dyspnea ventilation of the lung is less even than in health In favor of this conception, he advances the following evidence· He had the subject inspire from a spirometer containing hydrogen. The volume of hydrogen inspired, the volume expired in the following expiration, and the hydrogen content of the last portion of the expiration was determined From this data, he calculated the average air content of the lung, which he termed the effective middle capacity. A similar determination was carried out after five or six breaths assured more thorough mixing of the hydrogen; to this figure, Siebeck applied the term true middle capacity. He found that in health the effective middle capacity is about 80 per cent of the true middle capacity, while in cardiac failure this ratio is lowered to about 50 per cent Siebeck's interpretation of these findings is that the gas mixture in the lungs is much less uniform in cardiac patients than in health, and that a much larger fraction of the alveoli fail to be ventilated by a given inspiration To a large extent, this unevenness of pulmonary ventilation in cardiac failure is quite probably a consequence of the diminished elasticity of the lung discussed in the preceding section, and similar to what occurs in emphysema (page 532). Another factor that may play some part is narrowing of bronchioles due to passive congestion of their walls. It is evident that with uneven ventilation a smaller fraction of the air of each inspiration is utilized, which necessitates a larger volume of ventilation and thus predisposes to dyspnea.

4. *Shallow Breathing* —In the large majority of patients with cardiac dyspnea, respiration is very superficial, which must in itself result in a vicious cycle and further lower the efficiency of ventilation For the respired air consists of two parts (1) The air that fills the "dead space," *i e*, the nose, mouth, pharynx, trachea and bronchi, amounting to about 150 cc, which plays no part in aerating the blood, (2) actual exchange air which reaches the alveoli and aerates the blood There is evidence that the dead space may vary with the depth of respiration as a result of changes in the caliber of the bronchi, but the difference is apparently not great. There seems no reason to believe that the volume of the anatomical dead space is altered in cardiac dyspnea other than by this small adaptation. It is therefore obvious that the dead space constitutes a larger portion of the total respiratory volume when

breathing is superficial and thus lowers the efficiency of ventilation in cardiac dyspnea.

5. *Diminished Permeability of the Alveolar Walls.*—It is now almost universally agreed that the exchange of gases between the alveolar air and the blood occurs by the physical process of diffusion. The active secretion (by the alveolar cells) postulated by Haldane has not been demonstrated. In health, the diffusion of cardon dioxide occurs so rapidly that the tension of this gas is practically identical in the arterial blood and alveolar air; according to Bock[4] and his co-workers, it is only 0.2 mm higher in the arterial blood In the case of oxygen, such equality of pressure is not attained Although the arterial blood is about 96 per cent saturated with oxygen, Bock *et al* found that in health the partial pressure of this gas is from 18 to 62 mm. of mercury lower than in the alveolar air Presumably, one of the factors in this difference between oxygen and carbon dioxide is that the latter diffuses some 30 times more rapidly than oxygen

In cardiac dyspnea, the differences between the partial pressures of the respiratory gases in the alveolar air and the arterial blood may be very much greater than in health. That the arterial oxygen saturation and partial pressure is strikingly lowered in some, but by no means all, patients with cardiac dyspnea is well established (page 129). On the other hand, the oxygen content of the alveolar air is apt to be elevated in cardiacdyspnea (page 128). The difference between the arterial and alveolar oxygen tensions is most marked when pulmonary engorgement is of high degree, and is prone to be especially accentuated if there is coincident emphysema Thus, Kroetz[32] found that while in health the oxygen tension in the alveoli averages about 23 mm. ± 9 mm.Hg higher than in the arterial blood, in cardiac failure with severe pulmonary congestion the difference is of the order of 55 mm Hg. Even in aortic insufficiency and mitral stenosis without clinical manifestations of pulmonary stasis, and with arterial oxygen saturation either normal or not diminished below 91 per cent, Kroetz also found the difference between the arterial and alveolar tensions above his normal, averaging 36 mm.Hg

In the case of carbon dioxide, which diffuses so rapidly, the arterio-alveolar tension difference in heart failure is much less than that of oxygen, and is apparently significant only when pulmonary engorgement is very severe. In 4 patients with cardiac dyspnea, Peters and Barr[44] found the carbon dioxide tension of the arterial blood between 13 and 19 mm.Hg higher than that of the alveolar air. Similar results were obtained by Campbell, Hunt and Poulton[8] However, these investigators calculated the carbon dioxide tension of the arterial blood from the CO_2 combining curve of the venous blood and the CO_2 content of the arterial blood.

They assumed that the carbon dioxide absorbing powers of arterial and venous blood do not differ significantly. Later, it was shown by Meakins, Dautrebande and Fetter[37] that this assumption is invalid in cardiac failure with slowing of blood flow. They found that while the carbon dioxide combining power of the venous blood of such patients is diminished, that of the arterial blood is normal. Using the arterial blood for their studies. Meakins and his associates found that in mitral stenosis with heart failure the carbon dioxide tension of the arterial blood does not differ significantly from that of the alveolar air Kroetz also found the carbon dioxide tension equal in the arterial blood and alveolar air in valvular defects without clinical evidences of pulmonary stasis However, when these valvular defects were accompanied by moderate pulmonary engorgement the carbon dioxide tension of the arterial blood averaged 3 mm. Hg higher than that of the alveolar air, and in the presence of severe pulmonary congestion the difference was of the order of 9 mm.

Probably, several factors are summated in bringing about the abnormally great oxygen and carbon dioxide arterio-alveolar tension differences present in *some* instances of cardiac failure As a result of pulmonary rigidity and unequal ventilation of different parts of the lung, aeration of the blood passing the poorly ventilated alveoli is correspondingly impaired and contaminates that from the well-ventilated alveoli when mixed with it in the pulmonary artery. But in addition it seems probable that the alveolar walls in passive congestion offer greater resistance to the diffusion of the respiratory gases than in health, although it is difficult to evaluate this factor quantitatively The thickening and other changes observed histologically in the alveolar walls of the engorged lung suggest decrease in their permeability Certainly, the presence of transudate must interfere with the diffusion of gases Another fact that suggests decreased permeability is the increase in oxygen saturation of the arterial blood that may follow the inhalation of high concentrations of oxygen (page 739). Finally, the much greater increase in the arterio-alveolar oxygen difference than in that of the much more highly diffusible carbon dioxide is in accord with the conception of decreased permeability of the alveolar walls

6. *Reflex Acceleration of Breathing Initiated by Pulmonary Engorgement.*—While the total *volume* of ventilation is largely regulated by chemical mechanisms, reflex influences are of great significance in determining the *form* of breathing, *i. e*, the frequency and amplitude of the individual respirations Although these reflexes may arise in various parts of the body, the most important are believed to be initiated in the respiratory tract, from the nose to the alveoli, the muscles of respiration, and the thoracic articulations. In the study of the nervous control of

respiration, the focal point has been occupied by the Hering-Breuer theory of reflex autoregulation of respiration. According to this theory, when a certain distention of the alveoli has been attained, inspiration is reflexly terminated by impulses along the vagus; while when the alveoli have been adequately deflated, other vagal impulses initiate inspiration The theory has been variously modified (Hess[28]), but it seems probable that the mechanical factor of alveolar distention plays a part in determining the frequency and depth of respiration

There is evidence that this reflex mechanism is involved in the production of dyspnea Eppinger and Schiller[17] suggested that engorgement of the pulmonary circuit or increase in the carbon dioxide content of the alveolar air may reflexly stimulate respiration. The latter part of the hypothesis cannot be of general validity, for the carbon dioxide content of the alveolar air is characteristically lowered and not elevated in cardiac dyspnea. But the conception that pulmonary stasis reflexly stimulates respiration is very plausible and merits serious consideration

Evidence in favor of the importance of reflexes from the engorged lung in the production of cardiac dyspnea is adduced in the pioneer investigations of Harrison[23] and his associates, to whom appreciation of the significance of this factor is almost entirely due. In experiments on dogs, they found that reduction of the vital capacity of the lungs by pneumothorax, distention of the capillaries of one lung with blood, or introducing fluid into the lungs accelerated respiration, provided the vagus nerves were intact The chemical changes in the blood did not suffice to account for the acceleration of respiration On the other hand, in vagotomized dogs, reduction of vital capacity did not accelerate breathing unless the reduction of vital capacity was sufficient to produce marked oxygen deficiency or increased acidity of the blood This work of Harrison and his associates thus indicates very strongly that the tachypnea resulting from diminution in vital capacity is produced by a vagal reflex. And since decrease in vital capacity is characteristic of cardiac dyspnea, they attribute such reflex factors an essential rôle in the production of this form of shortness of breath The reflex acceleration of breathing in pulmonary engorgement is doubtless to be regarded as compensatory and beneficent, tending to atone for the decrease in vital capacity

Clinical Manifestations of the Impairment of External Respiration Due to Pulmonary Engorgement —In the foregoing, we have described the mechanisms through which pulmonary engorgement affects respiration. The following sections will be concerned with the clinical manifestations resulting from the operation of these mechanisms

The Minute Volume of Ventilation.—It has long been known that *the dyspneic cardiac patient breathes more air per minute than normal*

In some instances this hyperventilation is slight, but in others it is very marked. Peabody, Wentworth and Barker[41] found that the minute volume of ventilation averaged 8.5 liters in a group of individuals with severely decompensated heart disease and 6 liters in other cardiac patients in relatively good condition. In one of their patients, the minute volume of ventilation was halved when compensation was restored. It is true that in dyspneic individuals the basal metabolism is generally elevated, but the increase is not nearly adequate to account for the increment in ventilation Observation of the shallow breathing of most cardiac patients indicates immediately that the increased respiratory volume is accomplished by acceleration of the rate of breathing and not by greater depth. In fact, Peabody and his co-workers found that the average volume of the individual respirations was 408 cc in their decompensated patients and 471 cc in those with diseased but functionally more competent hearts. There are, however, exceptional forms of cardiac dyspnea with deep breathing, which will be referred to again (page 134).

The Vital Capacity.—The great significance of the increased minute volume of respiration for the production of dyspnea in heart disease becomes more evident in the light of the fact that *the greater air exchange is achieved in the face of decreased vital capacity.* As will be discussed later (page 223), the vital capacity of cardiac patients is decreased roughly in proportion to the severity of the dyspnea, and may be well below one-quarter of the normal value. Moreover, not only is the vital capacity of those with insufficient hearts decreased under the usual conditions of breathing, but even the strongest respiratory stimuli fail to increase ventilation to the same extent as in health. This is well shown in the rebreathing experiments of Peabody and of Peters and Barr.[44] They allowed normal controls and cardiac patients continuously to rebreathe their expired air so that the increasing concentration of carbon dioxide would induce hyperventilation and dyspnea. The rate and volume of respiration were measured until the increasing dyspnea became unbearable Peabody found that normals were able to double the rate and quadruple the volume of the respirations, thus increasing ventilation 8 times, the concentration of carbon dioxide in the inspired air exceeded 9 per cent at the end of the experiment. On the other hand, while the patients with cardiac insufficiency increased the rate of respiration almost as well as the normals, and responded with augmented ventilation to the lower concentrations as did the healthy subjects, the maximum respiratory volume attained when dyspnea forced cessation of the experiment was much lower than in health. At the end of the experiment, the minute volume of respiration averaged only about 3 times the initial volume. These experiments demonstrate that the decreased vital capacity

of pulmonary engorgement is not due to inadequate stimulation, for even under the influence of the most powerful respiratory stimulant, carbon dioxide, *the patient with heart failure is unable to increase the depth of breathing to nearly the same extent as in health.*

The Diminished Efficiency of Respiration in Heart Failure.—Kraus[31] observed that the carbon dioxide content of the expired air is lower in patients with cardiac dyspnea than in health. Beddard and Pembrey,[3] Peters and Barr,[43] and others have since demonstrated that the carbon dioxide content of the actual alveolar air is diminished in cardiac dyspnea It is true that Peters[42] found the alveolar carbon dioxide content normal in some instances of cardiac dyspnea, but even in these he observed that it was lower than normal in relation to the bicarbonate of the plasma. In severe shortness of breath, the carbon dioxide tension of the alveolar air may be only about one-half the normal. Furthermore, Peabody, Wentworth and Barker[41] found that the percentage of oxygen in the expired air is somewhat above the normal. Inasmuch as the total carbon dioxide elimination and oxygen consumption is usually above normal in these patients (page 129), the changes in the composition of the expired air are merely another indication that the total volume of air breathed per minute is increased in cardiac dyspnea.

These findings—increased minute volume of ventilation and decreased carbon dioxide and increased oxygen concentration in the expired air—show that *the efficiency of ventilation is decreased in cardiac dyspnea, less aeration of the blood being effected by each liter of air breathed than in health.*

The Rôle of Diminution in the Respiratory Factor of Safety in the Production of Exertional Dyspnea.—Because of decreased efficiency of ventilation, the individual with pulmonary engorgement breathes a larger minute volume of air for a given exertion than in health. This is accomplished in the face of limitation, as a result of the decreased vital capacity, in the maximum volume of ventilation of which he is capable. In other words, the respiratory factor of safety—the difference between the volume of air breathed per minute and the maximum minute volume of ventilation that the patient can possibly attain—is encroached upon from both ends, by increase of the former and decrease of the latter. When the gap is sufficiently narrowed, the patient experiences dyspnea ("the consciousness of the necessity for increased respiratory effort"—Meakins[36]), just as does the healthy man when he performs exercise entailing ventilation close to the maximum for the individual.

It would thus appear that *exertional dyspnea in pulmonary engorgement and in health are fundamentally similar.* But in the cardiac patient dyspnea appears at a lower level of activity, in severe cases even at rest, because his respiratory factor of safety is

already diminished by the factors described in the preceding paragraphs.

This conception of the nature of the exertional dyspnea of pulmonary engorgement, which is based on the classical investigations of Peabody cited above, has received strong quantitative support from recent studies of Harrison[26] and his associates They found that while the severity of cardiac dyspnea roughly parallels increase in volume of ventilation and decrease in vital capacity, it is much more closely proportional to the quotient: $\frac{\text{ventilation}}{\text{vital capacity}}$. They designate this ratio, determined with a correction for body weight, the *ventilation index*, and find that it is of practical value in patients with evidence of heart disease in determining whether the subjective symptoms of dyspnea is actually due to heart failure or is neurotic in origin.

Changes in the Chemical Composition of the Blood.—Until recent years, the conception was dominant that cardiac dyspnea is due to stimulation of the respiratory center by changes in the chemical composition of the blood It was thought that, as a result of inadequate pulmonary ventilation, carbon dioxide excess or oxygen deficit develops and stimulates the respiratory center Others attributed the stimulation of the respiratory center to increase in the hydrogen-ion concentration of the blood, due either to carbon dioxide retention or to increase in the lactic acid content of the blood (page 133). These chemical theories of cardiac dyspnea were largely based on the findings in patients with extremely severe heart failure, often almost moribund, and on analyses of venous blood. The latter is obviously inadequate, for it is the arterial blood that irrigates the respiratory center In recent years, numerous investigations of the pathogenesis of cardiac dyspnea have been published which are based on analysis of the arterial blood of patients with less advanced heart failure These studies have shown that changes in the chemical composition of the blood participate in the genesis of dyspnea in a much smaller proportion of cases with heart failure than had previously been believed

Anoxemia.—Decrease in the oxygen saturation of the arterial blood was formerly considered a powerful stimulant of the respiratory center In accord with Gesell's[20] conception that breathing is controlled by the state of the respiratory center itself, anoxemia was thought to stimulate ventilation through causing the accumulation of lactic acid and perhaps other fixed acid katabolites within the center. More recent work suggests that such stimulation of ventilation as is produced by anoxemia is effected, not through a direct action on the respiratory center, but through stimulation of the sensitive zones in the carotid sinus and aorta, from which the respiratory center is reflexly activated (*cf* page 137 and Starling[52])

However, Christie[7] points out that observations at high altitudes and in carbon monoxide poisoning indicate that anoxemia *per se* is not a powerful stimulant of ventilation, and even when of the utmost severity does not produce dyspnea akin to that seen in heart failure. On the basis of these considerations alone, it might be inferred that anoxemia is not the fundamental cause of cardiac dyspnea. This inference has been substantiated by recent clinical studies.

The oxygen saturation of the arterial blood is diminished below the normal value of about 95 per cent in some patients with cardiac dyspnea. Such arterial oxygen deficiency is apt to be especially marked in the presence of intense pulmonary congestion or if there is also a considerable degree of emphysema. Reduction of the arterial oxygen saturation to between 75 and 85 per cent is not rare in these patients. In extreme and unusual instances, the oxygen saturation of the arterial blood is as low as about 50 per cent, although such extreme anoxemia is probably almost always preterminal.

The findings of different investigators concerning the frequency of arterial anoxemia in cardiac dyspnea vary greatly. Harrop[21] found arterial anoxemia in 7 of 9 decompensated cardiacs, and further observed that in 4 of his patients the oxygen content of the arterial blood rose with returning compensation. Similarly, Barach and Woodwell[2] observed decreased oxygen saturation in each of 7 patients with decompensated heart disease, and Kroetz[32] in 20 of 26 such individuals. On the other hand, Meakins, Dautrebande and Fetter[37] found no evidence of diminished oxygen saturation of the arterial blood in mitral stenosis in the absence of pulmonary complications. And Fraser[18] noted decreased oxygen saturation in only 1 of 8 dyspneic patients with mitral stenosis and auricular fibrillation, while in but 1 of his 5 patients with cardiac failure in arterial hypertension was the oxygen saturation of the arterial blood under 90 per cent. Cullen, Harrison[10] and their co-workers found the arterial oxygen saturation within normal limits even after exercise in a series of patients with slight and moderate degrees of heart failure.

Doubtless, the differences in incidence of arterial anoxemia in cardiac dyspnea reported by these investigators are largely attributable to divergence in the type of clinical material. Well-marked arterial anoxemia is common in long-standing heart failure with considerable pulmonary changes, while it is exceptional in early cardiac insufficiency with little structural change in the lungs, even though dyspnea is severe. The important point in the present connection is that while notable anoxemia is common in cardiac dyspnea, *there are numerous other severely dyspneic patients in whom the percentage saturation of the arterial blood with oxygen is within normal limits, and in whom the dyspnea is therefore not to be attributed to anoxemia.*

Kroetz[23] believes it probable that oxygen want is present even in such cases of cardiac failure with quite high oxygen saturation of the arterial blood He points out that because of the flatness of the dissociation curve of oxyhemoglobin above 85 per cent saturation, small variations in oxygen saturation correspond to marked changes in oxygen pressure Of course, it is the oxygen *pressure* in the blood that determines the supply to the tissues. He points out that if the arterial blood becomes alkalotic through loss of carbon dioxide by hyperventilation, the resulting displacement of the dissociation curve of oxyhemoglobin also tends to lower the arterial oxygen pressure (however, Meakins, Dautrebande and Fetter[37] found the arterial oxyhemoglobin dissociation curve in cardiac dyspnea within the limits of normal). Kroetz claims to have demonstrated pathologically low arterial oxygen pressure (down to 55 or 65 mm Hg, as contrasted with a normal of between 75 and 100 mm) in patients with normal arterial oxygen saturation Nevertheless, in view of the technical difficulties in the measurement of the oxygen pressure of the arterial blood, confirmation of Kroetz's results is to be awaited before accepting the view that there is a deficient supply of oxygen to the tissues in cardiac patients with undiminished oxygen saturation of the arterial blood

Further evidence that anoxemia is not the fundamental cause of dyspnea in the left-sided heart failure of such conditions as mitral or aortic valvular disease or hypertension is afforded by the following not uncommon observation: The patients may be intensely dyspneic with little or no cyanosis during the stage of isolated failure of the left side of the heart But when the right ventricle also fails, dyspnea often lessens and orthopnea disappears *pari passu* with deepening of the cyanosis. This sequence of events indicates that the dyspnea of left heart failure parallels the engorgement of the pulmonary circuit rather than the oxygen saturation of the arterial blood.

While these findings show arterial anoxemia is not the primary mechanism of at least most instances of cardiac dyspnea, it is an important accessory factor in the cases with marked arterial oxygen deficiency. This is shown by the results of oxygen therapy. Barach and Woodwell,[2] Barach and Richards,[1] and many others have found that inhalation of high concentrations of oxygen often alleviates cardiac dyspnea. I have also observed this repeatedly. But in other instances, oxygen therapy has no striking effect on cardiac dyspnea even though it raises the oxygen saturation of the arterial blood and eliminates cyanosis.

Retention of Carbon Dioxide —Carbon dioxide is so powerful a respiratory stimulant that accumulation of this gas in the blood was early suggested as the cause of cardiac dyspnea. Elevation of the carbon dioxide content of the blood, according to the most widely held theory, stimulates respiration through increasing the intracellular acidity of the respiratory center by lessening the diffusion gradient between the cells and the blood so that carbonic acid accumulates in the center. Recent work (page 137) indicates that

carbon dioxide also stimulates respiration through the intermediacy of the carotid sinus and aorta

In a large series of patients with cardiac dyspnea, the carbon dioxide content of the arterial blood shows variations so great as to indicate that it is affected by opposing influences.

Where there is severe pulmonary congestion or other widespread lesions of the lung, the arterial carbon dioxide content may be elevated definitely above the normal values of between 40 and 55 volumes per cent. Such increase in the arterial carbon dioxide content is accompanied by well-marked anoxemia and is to be attributed to impairment of gas exchange in the lungs. Probably because of the far greater diffusibility of carbon dioxide, much more pronounced impairment of pulmonary gas exchange is required to produce retention of carbon dioxide than depression of the oxygen saturation of the blood According to Kroetz,[32] carbon dioxide retention appears only after the oxygen pressure of the arterial blood has fallen to about 40 or 45 mm Hg (his normal values are of the order of 77 mm Hg).

Much more often, however, in cardiac dyspnea not accompanied by extreme pulmonary changes, *the carbon dioxide tension of the arterial blood is below normal,* at times strikingly so (Harrop,[27] Meakins, Dautrebande and Fetter,[47] and Fraser[18]). In such cases, it has repeatedly been observed that with the return of compensation the arterial carbon dioxide content rises. Inasmuch as Dautrebande[12] has shown that the decreased carbon dioxide content of the arterial blood may accompany abnormally high concentration of carbon dioxide in the venous blood, it is then evidently a manifestation of hyperventilation. In most instances, as was shown by Fraser, Ross and Dreyer,[19] the decrease in carbon dioxide content of the arterial blood is not accompanied by a corresponding drop in the alkali reserve, so that arterial alkalosis results However, there are other examples of cardiac failure, usually very severe and with systemic venous engorgement, in which the lowering of carbon dioxide in the arterial blood is accompanied by depression of bicarbonate and acidosis. In such cases, a rise in the lactic and perhaps other fixed acids of the blood plays a substantial part in reducing the carbon dioxide tension.

Since the carbon dioxide tension of the arterial blood is reduced in many, indeed most, instances of cardiac dyspnea, respiratory stimulation by carbon dioxide cannot be considered a general and necessary cause of shortness of breath in heart disease. But in those exceptional cases in which extreme pulmonary congestion or complicating lesions of the lungs result in carbon dioxide retention, the latter may well play an important part in causing dyspnea.

Increase in Hydrogen-ion Concentration.—The acid-base equilibrium of the arterial blood is also affected by opposing influences in

cardiac failure. There may be alkalosis or acidosis. Either of these may be completely compensated so that the hydrogen-ion concentration of the blood is unaffected, but more often compensation is inadequate and the reaction is altered While older investigators, based on studies of the venous blood, thought acidosis characteristic of cardiac dyspnea, Fraser, Ross and Dreyer[19] found that *in most instances of cardiac dyspnea the hydrogen-ion concentration of the arterial blood is definitely lowered.* Subsequent investigations by Meakins, Fetter and Dautrebande,[37] Fraser[18] and others have shown that alkalosis of the arterial blood due to carbon dioxide deficit is indeed a very common finding in cardiac dyspnea, being apparently a consequence of hyperventilation In these cases, the alkali reserve is most often not correspondingly lowered so that the gaseous alkalosis is not compensated and the hydrogen-ion concentration of the arterial blood is depressed This was the case in 9 of 12 dyspneic patients with arterial alkalosis studied by Kroetz,[32] the alkalosis being fully compensated in only 3

In other instances of cardiac dyspnea, however, the arterial blood is not alkalotic and may even be definitely acidotic Such patients are generally severely ill and have systemic venous engorgement. They seem to fall into two overlapping groups. (1) In some of the cases, pulmonary gas exchange is so severely impaired that there is carbon dioxide retention This may be compensated by a corresponding rise in bicarbonate, akin to the compensatory rise in bicarbonate that Scott[49] found in emphysema, so that the reaction is unchanged Or the gaseous acidosis may be decompensated with increased hydrogen-ion concentration in the blood (2) In extremely severe cardiac failure, there may be accumulation of fixed acid in the blood with corresponding depression of bicarbonate. An important factor in the production of this fixed acidosis is an increase in the lactic acid content of the blood, as described by Meakins and Long[38] They found that the lactic acid of the blood in such individuals at rest may exceed 100 mg per cent, as contrasted with a normal value of under 25 mg per cent But it is to be emphasized that such striking increase in the lactic acid of the blood occurs only in the most severe cardiac failure, generally when the patients are almost moribund Meakins and Long found that during exercise the lactic acid content of the blood rises higher in heart failure than in health Although there is little direct evidence concerning its origin, the accumulation of lactic acid in the blood has been attributed to both defective resynthesis to glycogen in the muscles as a result of diminished volume flow of anoxemic blood, and decreased destruction in the liver in consequence of hepatic engorgement Especially in the heart failure of hypertensive individuals, renal retention may also contribute to fixed acidosis. Kroetz[32] described fixed acidosis in

heart failure and deep breathing like the Kussmaul breathing of diabetes or uremia, but in most of the patients of this type that I have seen the respiration was rather superficial; presumably, the pulmonary engorgement mechanically inhibited deep breathing. Of course, both carbon dioxide retention and accumulation of fixed acids may co-exist

It seems evident from the preceding that cardiac dyspnea is fundamentally not an "acidotic dyspnea," for most often the arterial blood is alkalotic. In fact, the alkalosis is most often decompensated with lowered hydrogen-ion concentration in the arterial blood. But in those instances in which severe pulmonary lesions result in carbon dioxide retention with gaseous acidosis, or in which there is great elevation of lactic or other fixed acid in the blood, the increased hydrogen-ion concentration of the blood doubtless plays a part in producing the dyspnea. Such cases, however, are the exception and not the rule. And the acidosis is almost always a late development, superadded to other causes of dyspnea previously present.

The Reaction of the Venous Blood in Heart Failure.—The above discussion has been confined largely to the arterial blood, because this nourishes the respiratory center and is thus of primary significance in connection with the chemical causation of dyspnea Here a few words may be intercalated concerning the reaction of the venous blood in relation to that of the arterial blood in heart failure

When the cardiac output is decreased, it is obvious that the normal differences in oxygen and carbon dioxide content between the arterial and the mixed venous blood are correspondingly accentuated Indeed, the difference must usually be even greater than would correspond to the decrease in cardiac output, for the basal metabolism is usually increased in heart failure. With a decreased minute volume of the heart, the arteriovenous differences other than those of oxygen and carbon dioxide must also be increased, but these have hardly been studied

Dautrebande, Davies and Meakins[14] found that venous stasis increases the transit of water, chloride, and bicarbonate to the tissues They believe this transit of bicarbonate from the blood to the tissues is the principal factor in producing the lowered alkali reserve of the venous blood demonstrated by Peters and Barr[43] in some patients with cardiac dyspnea

The net result of these consequences of retarded blood flow—especially the increased carbon dioxide content and decreased alkali reserve of the venous blood—has been shown by Meakins, Dautrebande and Fetter,[37] Dautrebande,[12] and others to be a relative increase in the acidity of the venous as compared to the arterial blood The increased acidity of the venous blood in cardiac failure was long ago demonstrated by Lewis[31] and his co-workers in the course of their studies on the oxyhemoglobin dissociation curve Characteristic of slowing of blood flow is that the venous blood is so much more acid than the arterial. Thus, while Peters, Barr and Rule[45] found that in health the difference in pH between the arterial and venous blood is only 0 02 to 0 03, Dautrebande observed that in severe cardiac failure the pH of venous blood averages 0.15 less than that of arterial In health, the pH of the arterial blood averages 7 35 and that of the venous blood 7 33, while in cardiac failure Dautrebande found an

average arterial pH of 7.4 and an average venous pH of 7.25. In other words, Dautrebande and his co-workers have demonstrated that *in cardiac failure venous acidosis may accompany arterial alkalosis*. The arterial alkalosis is a manifestation of hyperventilation and consequent increased loss of carbon dioxide *via* the lungs and the venous acidosis results from slowing of blood flow in the tissues.

Diminution of Cardiac Output and of Blood Flow Through the Respiratory Center.—Experimental evidence (see Schmidt[45] and Gesell[20]) shows that diminution of blood flow through the medulla increases ventilation by stimulation of the respiratory center. Such a mechanism has been invoked as a cause of cardiac dyspnea by Fraser.[18] He points out that the combination of normal oxygen saturation and decreased carbon dioxide content of the arterial blood in many cases of cardiac dyspnea is just what one would anticipate as a consequence of hyperventilation produced by slowing of medullary blood flow. In accord with this conception, McMichael's[34] findings in a small number of cases indicate that diminished cerebral blood flow does occur in association with cardiac hyperpnea.

Attractive as is the explanation of cardiac dyspnea as a manifestation of inadequate cerebral blood flow, it does not obtain in a high proportion of the cases. In the first place, clinical experience shows that there is no close parallelism between retardation or systemic blood flow and dyspnea. Many patients with insufficiency of the left side of the heart resulting from hypertension or mitral or aortic disease have severe pulmonary engorgement with dyspnea on slight exertion or even at rest despite the fact that the absence of cyanosis and the warm extremities bespeak little, if any, showing of systemic blood flow. When the right ventricle finally fails in such individuals, there can be no doubt that systemic blood flow is further retarded, yet dyspnea often becomes less severe (page 529). Clinical observation thus leaves little room for doubt that dyspnea is much more closely linked to the severity of pulmonary engorgement than to slowing of systemic blood flow. While available methods for measuring the cardiac output in patients with engorged lungs are not entirely reliable, such results as have been obtained (see Chapter II) indicate that in *some* individuals with cardiac dyspnea, the minute volume is normal or decreased but insignificantly. And it would seem probable from what has been found in shock (page 631) that when cardiac output is diminished, the brain is among the last organs to have its blood supply cut down, the organism endeavoring to protect the brain and other immediately vital parts by vasoconstriction in the extremities. Finally, direct evidence that cerebral blood flow is not retarded in some patients with cardiac dyspnea has been obtained by Cullen, Harrison[11] and their associates. They made compara-

tive observations on the oxygen and carbon dioxide contents of the arterial and the internal jugular bloods of patients with heart failure, and found that the arteriovenous difference was not increased, as would be anticipated were cerebral blood flow slowed. It might be thought that the greater blood supply to the extremities during muscular exercise entails insufficient blood flow to the brain and thus provokes exertional dyspnea. But this is also disproved by the above-mentioned studies of Cullen, Harrison *et al.*, for they found that in cardiac patients the arteriovenous gas differences in the cerebral vessels were little affected by moderate exercise.

It thus seems evident that diminished cardiac output and cerebral blood flow are not concerned in the pathogenesis of many instances of cardiac dyspnea But these factors probably play a considerable rôle in the cases of severe heart failure in which the cardiac output is markedly diminished. For one thing, decreased volume of circulation may be concerned in the production of oxygen deficiency and carbon dioxide and lactic acid excess in the respiratory center with resultant stimulation of this center. And further if cerebral flow is cut down when cardiac output is greatly diminished, this would intensify the stimulation of the respiratory center by changes in the chemical composition of the arterial blood due to inadequate pulmonary ventilation In hypertensive patients with marked cerebral arteriosclerosis, it is to be presumed that the effects of even slight diminution in cardiac output on cerebral blood flow would be especially pronounced.

Nervous Factors in Exertional Dyspnea.—While older investigators regarded cardiac dyspnea as a disturbance in the chemical regulation of respiration, more recent studies have brought out the primary importance of aberrations in the nervous control of respiration evoked by the abnormal distribution of blood. Unfortunately, comprehension of the more intimate nature of these disturbances in nervous control is as yet in its infancy.

Reflexes —Of these, the most important seems to be the vagal reflex increase in ventilation shown by Harrison[23] and his associates to result from pulmonary engorgement (page 126). This reflex is doubtless significant in the pathogenesis of the dyspnea of left-sided heart failure, clinically the most common type.

Harrison[24] and his associates also found that ventilation immediately increased when they elevated the pressure in the venæ cavæ, either by intravenous infusion or the inflation of a balloon in the right auricle The reflex nature of this increase in ventilation was shown by their observation that it no longer occurred after the vagi were severed. This reflex presumably is concerned in the causation of dyspnea when venous pressure is increased as a result of right-sided heart failure.

Another type of reflex which may be concerned in the production of hyperpnea and consequent dyspnea in circulatory failure is that initiated in the sensitive zones of the *carotid sinus* and the root of the *aorta*. Heymans[29] has shown that such reflexes play an important part in the regulation of respiration. He found that perfusion of the carotid sinus with blood containing an excess of carbon dioxide or deficient in oxygen produces hyperpnea, while apnea results when the perfusion fluid is deficient in carbon dioxide. Experiments by Selladurai and Wright[50] indicate that the hyperpnea produced by anoxemia is due, not to direct stimulation of the respiratory center, as has long been believed, but rather to a vagal reflex initiated by stimulation of the carotid sinus. On the basis of this recent work, it would seem that when anoxemia is concerned in the genesis of cardiac dyspnea, it acts on the carotid sinus and aorta rather than directly on the respiratory center, while carbon dioxide retention stimulates both the sensory zones in the arteries and the respiratory center. Since it has also been found that fall in pressure within the carotid sinus and aorta reflexly stimulates ventilation, it is possible that the low arterial pressure present in peripheral circulatory failure (shock) is partly responsible for the hyperpnea of shock

The Respiratory Center.—Apart from the therapeutic effects of morphine and other drugs, little is known about the effects of circulatory disturbances on the *sensitivity* of the respiratory center. While extreme anoxemia paralyzes the respiratory center, moderate changes in the blood gases apparently have little effect on the sensitivity; at least, Macleod and Page[35] found that the sensitivity of the respiratory center to afferent nerve stimulation is not changed during the hyperpnea induced by breathing atmospheres poor in oxygen or rich in carbon dioxide

Comparing the chemical findings in the blood with the severity of dyspnea and the volume of ventilation, Peters and Barr[43] found indications of relative insensitiveness of the respiratory center in some patients with cardiac failure It is indeed striking that many individuals with long-standing right heart failure, especially when this is secondary to chronic pulmonary disease, have little dyspnea and no orthopnea despite marked cyanosis, high venous pressure and massive edema. Uhlenbruck and Merbeck[55] found that the ventilation reaction of such patients to the inhalation of low concentrations of oxygen and high percentages of carbon dioxide is less marked than that of normals. They consider this evidence of decreased sensitivity of the respiratory center. But it is also possible that changes in the composition of the blood or impaired gas exchange in the lungs causes the lessened reaction. In emphysema, for example, it is known that the alkali reserve of the blood may be increased to compensate for the carbon dioxide retention,

which may account for the relative sluggishness of the reaction to the inhalation of carbon dioxide. As yet, it would seem that there is no unequivocal evidence of change in the sensitivity of the respiratory center in circulatory failure before the terminal paralysis.

The Registration of Air Want on Consciousness.—We have seen that the sensation of dyspnea arises when the actual and necessary ventilation approaches close to the maximum feasible ventilation, whether because of increase in the former or decrease in the latter. But the nature of the sensations comprised in the feeling of dyspnea, like those of hunger, thirst, etc., have not been clearly elucidated. Goldscheider, Joachimoglu and Rost,[21] who have studied the sensations aroused by the inhalation of carbon dioxide, believe that the feeling of pressure in the epigastrium, chest and neck so characteristic of dyspnea arises in the muscles of the chest wall and diaphragm. They consider the sensation a manifestation of increased tonus of these muscles. There is probably also an element of muscular fatigue in the sensation, occasioned by the lessened rest period of the respiratory muscles in tachypnea and the necessity for active muscular work in expiration as a result of the rigidity of the engorged lung. But the fact that sensations akin to those of cardiac dyspnea are experienced when one holds his breath sufficiently long indicates that the work of the respiratory muscles is not the only factor in the production of the sensation. With severe dyspnea, there is also the often terrifying realization by the patient that he cannot hold his breath. Probably, dyspnea is a complex sensation in which various sensory impressions are summated.

General Discussion of the Pathogenesis of Exertional Dyspnea.—The foregoing may serve to indicate the complexity of the problems of cardiac dyspnea and the fragmentary state of present knowledge Circulatory failure sets in motion a multiplicity of mechanisms which derange the regulation of respiration so as to evoke dyspnea. They fall into five general groups:

1. Impairment of the ventilation of the lungs due to pulmonary engorgement. Hydrothorax, ascites or swelling of the liver may also interfere with the respiratory movements

2. Changes in the chemical composition of the blood—anoxemia, carbon dioxide retention, and accumulation of lactic acid—resulting from inadequate aeration of the blood in the lungs and/or slowing of blood flow through the tissues; these stimulate the respiratory center and sensitive areas in the carotid sinus and aorta so as to increase ventilation

3 Slowing of blood flow through the respiratory center, which stimulates the latter.

4. Engorgement of the systemic veins, which reflexly stimulates respiration.

5. Fall in pressure in the aorta and carotid sinus, which also reflexly stimulates respiration

The significance of each of these factors varies greatly in different types of circulatory failure.

Exertional Dyspnea in Left-sided Heart Failure.—Much the most common forms of heart failure are those which start as isolated insufficiency of the left side of the heart, they include hypertensive and arteriosclerotic heart disease and mitral and aortic valvular defects Exertional dyspnea is usually the chief initial complaint and may be agonizing in severity, even at rest During the stage of isolated insufficiency of the left heart, when systemic venous engorgement is absent, examination of the arterial blood generally reveals undiminished oxygen saturation, normal lactic acid content and alkali reserve, decreased carbon dioxide content, and lowered hydrogen-ion concentration. The two latter changes are obviously *consequences* of the hyperpnea, and it is obvious that the dyspnea is not due to changes in the chemical composition of the blood. The frequent absence of cyanosis and coldness of the extremities indicates little, if any, retardation of systemic blood flow, a conclusion which has been supported in a few instances by measurements of cardiac output Since the blood flow through the extremities is not retarded notably, it seems a fair assumption, apart from patients with cerebral arteriosclerosis, that the same is true of cerebral blood flow Slowing of blood flow through the respiratory center is therefore not the essential cause of the dyspnea Inasmuch as the arterial and venous pressures are usually unchanged in these patients, reflex stimulation of the respiratory center from the carotid sinus or great veins does not come into question

Since none of these mechanisms applies, we must turn for the explanation of the dyspnea of isolated failure of the left heart to the pulmonary engorgement which is the invariable characteristic of this form of circulatory insufficiency Clinical observation shows that in left-sided failure, apart from depression of the respiratory center by morphine, *the severity of the dyspnea waxes and wanes with the intensity of the pulmonary engorgement* All available evidence indicates that the dyspnea of left-sided heart failure is primarily a symptom of pulmonary engorgement.

The individual mechanisms through which pulmonary engorgement induces dyspnea have already been described (pages 122, 136), and will here be only briefly summarized in their relation to one another. Pulmonary engorgement entails exertional dyspnea because it forces the patient to ventilate at a rate close to the maximum of which he is capable. This impairment of the respiratory reserve is due both to an increase in the actual volume of ventilation and a decrease in the vital capacity, of which the maximum possible ventilation is a function.

Pulmonary engorgement *increases* ventilation because:

1. It diminishes the elasticity of the lung, as a result of which breathing is shallow and uneven. With shallow breathing, the dead space forms a larger fraction of the tidal air, so that a greater portion is wasted. Similarly, uneven ventilation entails less efficient utilization of the tidal air

2 Where pulmonary engorgement diminishes the permeability of the lung through changes in the alveolar walls and the accumulation of fluid in the alveolar spaces—as manifested by abnormally great hemo-alveolar gas differences—increase in ventilation will help to maintain these hemo-alveolar differences and thus counteract the lessened permeability of the pulmonary barrier.

3. Harrison[22] has shown that pulmonary engorgement increases ventilation through a vagal reflex

4 Most patients with heart failure have increased basal metabolism, which necessitates correspondingly greater ventilation. While this increase in basal metabolism is partially a *consequence* of the hyperpnea, resulting from the increased work of the respiratory muscles, it in turn demands an increment in ventilation.

Pulmonary engorgement *decreases* vital capacity through:

1. Diminution in the elasticity of the lungs

2. Diminution in the volume of the air spaces resulting from swelling of the alveolar walls, protrusion of ectatic capillaries into the alveolar lumens, and transudation of fluid into the alveoli.

Through these changes in the lungs, pulmonary engorgement results in actual ventilation approaching the maximum possible ventilation so closely that there is respiratory embarrassment, subjectively translated as dyspnea. When the engorgement is slight, dyspnea appears only when ventilation is increased as a result of exercise or excitement But with severe engorgement, even resting ventilation approaches the maximum of which the subject is capable and there is dyspnea under basal conditions.

In most instances of isolated left heart failure, pulmonary engorgement *per se* seems to account adequately for the exertional dyspnea in the fashion just described When left-sided failure is so severe that cardiac output is greatly diminished, it is to be presumed that diminished blood flow through the respiratory center may play an accessory rôle in the causation of the dyspnea. This seems especially plausible in patients with marked cerebral arteriosclerosis, a common complication in hypertensive and arteriosclerotic heart disease. And when pulmonary engorgement is complicated by bronchopneumonia, extensive pulmonary infarction, or pulmonary edema, arterial anoxemia and far more rarely carbon dioxide retention may develop and participate in the production of the dyspnea.

Exertional Dyspnea in Right Ventricular Failure.—Insufficiency of the right ventricle with systemic venous stasis is most often secon-

dary to pre-existent left-sided failure. In such cases, the pulmonary engorgement continues to operate as a cause of dyspnea, but the failure of the right ventricle also tends to produce dyspnea through several mechanisms:

1. As a result of the slowing of systemic blood flow, the blood returns to the lungs abnormally poor in oxygen and rich in carbon dioxide. If pulmonary aeration is sufficiently impaired because of engorgement due to the antecedent left-sided failure, this will not be overcome in the lungs, with resultant arterial anoxemia and much less often carbon dioxide excess. In severe right-sided failure, there may also be marked increase in the lactic acid content of the blood with resultant decrease in alkali reserve, the accumulation of lactic acid is presumably attributable to both engorgement of the liver with injury to hepatic function and retarded circulation of anoxemic blood through the muscles These chemical changes in the blood may well be significant in the production of dyspnea

2. The cold extremities and small oscillometric excursions often indicate that cardiac output is decreased, a conception which is fortified by most of the measurements of cardiac output which have been published, although the validity of the latter is not beyond question. With such small cardiac output, it is possible that the blood flow through the respiratory center is significantly decreased.

3 According to Harrison, the rise in pressure in the right auricle and venæ cavæ reflexly stimulates respiration (page 136).

4 Hydrothorax and ascites may be important causes of dyspnea in right ventricular failure The same is true of rapid swelling of the liver which renders deep breathing painful

It is noteworthy that when right ventricular failure complicates pre-existent left-sided failure, dyspnea is often ameliorated and orthopnea may disappear, evidently, the relief of pulmonary engorgement outweighs the causes of dyspnea due to the right-sided failure

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ADDENDUM

OXIDATIVE METABOLISM AND BODY TEMPERATURE

Basal Metabolism.—Peabody, Meyer and Du Bois[40] and Peabody, Wentworth and Barker[41] showed that in heart failure the basal metabolism is increased On the other hand, they found that in compensated heart disease the metabolic rate is not augmented, indicating that the rise in metabolism is actually due to the heart failure and not to the cardiac disease *per se* Resnik and Friedman[46] found *an average metabolic rate of +32 per cent in heart failure,* with variation between +15 and +60 per cent, with improvement

of the circulation the basal metabolism fell, further evidence that the enhanced metabolism is a consequence of heart failure.

The above-mentioned investigators and Du Bois[15] believe the *greater oxygen consumption in heart failure is due principally* to the increased work of the muscles of respiration The latter results from pulmonary engorgement in two ways. (1) Pulmonary engorgement entails an increase in the minute volume of ventilation (page 126) That increase in ventilation results in greater oxygen consumption has been shown by measurements in hyperventilation produced either voluntarily or by inhalation of carbon dioxide (Resnik and Friedman[46]) (2) And perhaps even more important than the greater volume of ventilation in increasing the work of the muscles of respiration and consequently oxygen consumption, is the greater rigidity of the lung which results from engorgement (page 122) Because of the lessened elasticity of the engorged lung, more muscular work is necessary for a given volume of ventilation.

It would thus appear that the increased metabolic rate of heart failure is primarily a consequence of pulmonary engorgement and *consequently of failure of the left side of the heart* In accord with this conception, Resnik and Friedman observed metabolic rates below zero in 3 instances of constrictive pericarditis with pronounced systemic venous engorgement but apparently not severe pulmonary engorgement since dyspnea at rest was not prominent The greatly increased oxygen consumption of the hypertrophied and dilated heart (page 332) may also add appreciably to the oxygen consumption in some cases, according to calculations of Resnik and Friedman, this factor may account for an increment of perhaps as much as 20 per cent of the total metabolism

Effect of Exercise on Oxygen Consumption in Heart Failure.— Not only is the basal metabolism increased in heart failure, but the increment in oxygen consumption during exercise is also augmented above the normal (Campbell and Sale[9]) This augmentation is not great and is probably largely due to the increment in the work of *the muscles of respiration during exercise being relatively greater* than that of the healthy person. Observations by Meakins and Long[38] and Campbell and Sale indicate that the increased oxygen consumption during exercise in heart failure is effected in the *manner that would be anticipated* as a *result* of *inability* to augment the output of the heart as much as normally. At the start of the exercise the oxygen consumption does not mount as rapidly as in the healthy person. Furthermore, the cardiac patient consumes a smaller proportion of the total oxygen requirement for the exercise during the actual exercise and a larger proportion after cessation *i. e.*, he acquires a larger *oxygen debt* than is the case in health for the same exercise. The individual with heart failure thus requires

a longer time after stopping exercise for the oxygen consumption to fall to normal.

While oxygen consumption and oxygen debt for exercise within the capacity of the cardiac patient are thus greater than in health, Meakins and Long and Harrison and Pilcher[25] have shown that the *maximum* oxygen consumption and debt of which the individual is capable are decreased in heart failure The lessened height to which the cardiac patient can elevate oxygen consumption is doubtless a consequence of the smaller cardiac output which he can attain. The smaller maximum oxygen debt is presumably due to inhibition of exercise as a result of dyspnea at a lower level than in health. Since the oxygen debt represents the amount of oxygen required for the oxidation of that part of the lactic acid formed in the muscles which is not resynthesized to glycogen, the oxygen debt cannot become large in heart failure because pulmonary engorgement and the resultant dyspnea force cessation of exercise before much lactic acid and a correspondingly large oxygen debt accumulates.

Elimination of Carbon Dioxide in Heart Failure.—According to Campbell and Sale,[6] the changes in carbon dioxide elimination in heart failure are similar to those in oxygen consumption. The cardiac patient forms more carbon dioxide for a given exercise than does the healthy person, increases the excretion of carbon dioxide at the start of exercise more slowly, excretes a higher proportion of the carbon dioxide after the exercise is over, and continues to eliminate an increased amount of carbon dioxide for a longer time after the cessation of exercise. The smaller percentage of carbon dioxide in the expired air in heart failure has already been mentioned (page 128).

Eppinger's Metabolic Theory of Heart Failure.—In the foregoing, the metabolic changes in heart failure have been described as consequences of the cardiac insufficiency. Eppinger and his associates have advocated the reverse conception, *i e*, that the metabolic changes are primary and produce cardiac failure. They found that oxidative metabolism in patients with heart failure is what they term "uneconomical" This uneconomical metabolism is manifested by deficient resynthesis of lactic acid to glycogen and diminished buffering power in the muscles Eppinger believes that as a result of this metabolic aberration, a higher cardiac output is entailed, which naturally elevates the work of the heart and thus causes it to fail Eppinger also believes that the metabolic changes may involve not only the skeletal muscle but also the heart In confirmation of this conception of a general metabolic causation of heart failure, Eppinger[16] and his associates found that in the early stages of heart failure the cardiac output is not only not decreased but actually increased

However, subsequent investigations have disproved some of Eppinger's contentions The cardiac output in heart failure (see Chapter II) is not

increased in heart failure but tends to be decreased (except for some cases of hyperthyroidism), although for a time compensatory mechanisms may maintain it at its previous level. Moreover, the deficiency in the resynthesis of lactic acid to glycogen described by Eppinger is logically explained as a result and not a cause of heart failure, due to the slowing of blood flow through the muscles and liver resulting from the cardiac weakness. However, it is plausible, though not proved, that once such metabolic abnormalities have resulted from heart failure, they may in turn injure the functional capacity or increase the work of the heart There may thus result a secondary deleterious effect on the circulation, of the nature of a vicious circle, which may increase the degree of decompensation

Body Temperature.—Fever is common in patients with heart failure severe enough to require bed rest. When high, some such cause as active rheumatic infection, bacterial endocarditis, pneumonia, or infarction is usually revealed as the cause Kinsey and White[30] were almost always able to demonstrate some such cause for elevation of over 1 degree in patients with heart failure. But sometimes slight or moderate elevation of temperature exists and yet careful investigation reveals no other cause than the circulatory insufficiency Thus, Cohn and Steele[8] found that of 172 persons with heart failure 153 exhibited on two or more occasions a rectal temperature of at least 100° F , in 49 of these, no cause for the fever other than heart failure was discovered In a number of instances, Cohn and Steele were able to show that the heart failure appeared just prior to the fever, while with improvement both disappeared simultaneously.

That heart failure may entail pyrexia is not surprising. It has just been seen that in heart failure oxygen consumption and consequently heat production is generally increased. At the same time the mechanism for the dissipation of heat may be impaired For when cardiac output is diminished, blood flow through the skin, which plays so important a part in the dissipation of body heat, is decreased Indeed, the diminution in blood flow through the skin is probably proportionately greater than the decrease in cardiac output, for experimental evidence obtained in shock (page 631)—which probably also applies to diminished cardiac output due to heart failure—indicates that when cardiac output is lessened, peripheral vasoconstriction results in greater cutting down of blood flow through distal parts than through the vital organs. This is probably largely responsible for the frequent finding in heart failure of cold extremities despite elevated rectal temperature. In accord with this conception, Steele[53] has found that the difference between rectal and surface temperature is greater in heart failure than with unimpaired circulation.

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CHAPTER VIII

PAROXYSMAL DYSPNEA

In the first systematic treatise on diseases of the heart published in the English language, Hope[8] gave a classical description of asthmatic paroxysms due to cardiac disorder This variety of paroxysmal dyspnea has since been known as cardiac asthma, and indeed the attack may simulate bronchial asthma so closely as to occasion serious diagnostic difficulties In contradistinction to the continuous exertional dyspnea described in the preceding chapter, cardiac asthma is characterized by paroxysmal occurrence without obvious exciting cause in the form of increased physical exertion. While most patients with cardiac asthma also have exertional dyspnea, the freedom of others from shortness of breath on exertion is remarkable. Thus, a woman took long walks in the early evening without discomfort, but was often awakened from her sleep by a paroxysm of dyspnea.

The Attack.—Few clinical pictures are more dramatic and terrifying to both patient and onlooker than a severe paroxysm of cardiac asthma. It occurs most often in the night, generally in the first hours after the patient has fallen asleep Sometimes, patients state that the attack came on before they were completely asleep but were only dozing; this is especially apt to occur when hypnotics have been administered Diurnal attacks are also most common when the subject is sleeping In 94 per cent of Pratt's[14] cases, the initial seizure of cardiac asthma occurred while the patient was quiet in bed. However, although less commonly, a severe paroxysm may develop while he is wide awake, even engaged in a conversation. Of course, such attacks are not as readily differentiated from exertional dyspnea. The same is true of attacks appearing shortly after a hearty meal

The usual description given by the patient is that he awakened from sleep with a sense of anxiety and suffocation Most often he states that the preceding sleep was sound but occasionally disturbing dreams are recalled and blamed for the seizure In the mildest attacks, a few deep breaths and perhaps the coughing up of a little viscid sputum dispel the sense of suffocation and the patient drops back to sleep within a few minutes The seizure may be initiated by cough; in individuals in whom this occurs repeatedly, the administration of morphine when cough alone is present may abort the full-fledged attack. Pratt describes as "equivalents" of cardiac asthma paroxysmal nocturnal anxiety and cough. The nature of such mild attacks or equivalents, which the sufferer may disregard

and reveal only on close questioning, becomes clear only when a typical seizure occurs.

In more severe paroxysms, the dyspnea is intense. The patient sits upright in bed grasping the sides to aid the accessory muscles of respiration by fixing the shoulder girdle. Often, he insists on letting his legs hang down from the side of the bed (the rationale of this, as will be seen below, is probably that it diminishes the venous return to the heart) Not uncommonly, the sufferer leaves the bed for a chair or he goes to the window like one in an attack of bronchial asthma. The breathing is very rapid, and while it has seemed superficial in the attacks that I have seen, Hofbauer[7] has published pneumographic tracings of both superficial and deep respiration. Wassermann[18] has also obtained tracings showing deep respirations Most often, the breathing at the height of the attack is regular, but occasionally there is some irregularity and there may be a tendency to periodic breathing Often, the breathing is not especially noisy, but in other cases wheezing is audible at a distance as in bronchial asthma The air hunger may be so intense that the patient will not interrupt his breathing for even an instant to answer a question The face often bears an agonized expression; after the seizure the victim may tell of a fear of suffocation akin to the *angor animi* of angina pectoris, and state that while at the onset he simply felt that he could not breathe deeply enough, later the sensation was that of strangulation. Or he may awaken with the feeling that a cord is being tightened about his neck. Pain is absent in the vast majority of attacks of cardiac asthma, but there are cases in which individual seizures follow or are combined with anginal pain

A short cough may occasionally interrupt the breathing. With it may be brought up a little viscid sputum, which is sometimes bloody The expectoration may signal the termination of the attack In many seizures there is no expectoration. On the other hand, if pulmonary edema becomes pronounced, large volumes of the characteristic pink, frothy, albuminous sputum may be brought up

At the beginning of the seizure, the patient is generally rather pale. But if the attack lasts any considerable time, and especially if pulmonary edema becomes copious, cyanosis appears and deepens With the peripheral circulatory collapse that may prove a terminating complication, the cyanosis becomes grayish and often patchy. The skin is frequently covered by a cold sweat and feels clammy.

The findings on physical examination of the chest vary greatly. In many cases no abnormality other than rapid breathing is detected. The chest is often distended during the attack like in bronchial asthma, this may be accompanied by a hyperresonant percussion note, prolongation of expiration, and sonorous and sibilant râles,

so that the findings are practically identical with those of bronchial asthma. In several such cases, only the history and subsequent course convinced me that I was dealing with cardiac asthma. With the development of pulmonary edema, the characteristic moist râles appear. These are usually first heard at the bases and most often do not progress further. But in other cases they spread throughout the lungs. I have several times heard the râles of pulmonary edema anteriorly when they were not audible at the bases.

Auscultation of the heart is often difficult because of the noisy breath sounds and râles The cardiac signs naturally vary with the disease in which the paroxysm develops Generally, the pulmonic second sound is strikingly accentuated, testifying to the hypertension in the lesser circulation It is not uncommon to hear gallop rhythm during the attack which is no longer audible the next morning.

The pulse is most often rapid and small. However, there are also instances in which the pulse is slow. I recently saw a case of aortic stenosis and insufficiency in which, despite copious pulmonary edema, the pulse rate was only 60 per minute, decidedly slower than its usual rate. The tension varies and is discussed below On rare *occasions, pulsus alternans is a transitory phenomenon during* the attack.

The Arterial Pressure.—The behavior of the arterial pressure varies greatly in different attacks It is apparently affected by two opposing influences, namely, diminished output of the left ventricle, which tends to lower the arterial pressure, and peripheral vasoconstriction resulting from asphyxia and perhaps also reflexly induced by the diminution in cardiac output which works in the direction of elevation of pressure. In many instances, as observed by Pratt, Amblard,[1] Wassermann, and others, the resultant is a rise in arterial pressure; this was very striking in a number of cases in which I followed the course of the pressure during and after the attack The asphyxia of pulmonary edema is apt to induce an especially marked rise in pressure, which may exceed 70 mm Elevation of pressure has occurred in a large majority of the attacks of cardiac asthma that I have seen On the other hand, there are also cases in which the diminished left ventricular output predominates and the arterial pressure falls A marked and progressive fall in blood pressure accompanied by coldness of the extremities, graying of the cyanosis, and cold perspiration is naturally of most serious omen; however, some patients survive many such attacks.

The Venous Pressure.—In many paroxysms, even of great severity, the veins of the neck are not distended. In a number of such patients, I have found by direct measurement that the venous pressure was not increased, showing immediately that the cardiac

failure implicated the left side of the heart alone But in other instances the embarrassment of respiration is accompanied by mighty bulging of the cervical veins and the pressure in the veins of the arm rises very high—over 30 cm of water in 2 cases. With the cessation of the paroxysm, or its termination by the injection of morphine, the venous pressure quickly returns to its previous value. In such instances, the rise in venous pressure is evidently a *consequence* of the respiratory disturbance; the same phenomenon is often observed in bronchial asthma That certain varieties of dyspneic breathing elevate the venous pressure has been shown experimentally by Herbst [6] He rendered healthy men severely dyspneic by means of a mechanical hindrance to breathing and found that the venous pressure rose to over 20 cm of water. The mechanism of the rise in venous pressure in such cases is evidently that the obstruction to expiration entails an elevation of the intrapleural pressure, which in turn offers an impediment to the return flow in the great veins The predominantly expiratory nature of the respiratory difficulty in cardiac asthma is often obvious. It is readily understood how increased rigidity of the lung due to engorgement or the presence of transudate in the small bronchi necessitate more powerful expiration As already mentioned, when the elevation of venous pressure is a consequence of the dyspneic paroxysms, the venous tension returns to normal after the cessation of the attack. However, attacks of cardiac asthma also occur, although much less often, in the presence of continuously elevated venous pressure due to insufficiency of the right heart. During the attack. there is generally an additional rise in venous pressure. In such instances of cardiac asthma with continuously elevated venous pressure, the weakness of the right heart is not isolated but is associated with weakness of the left heart. That the left-sided failure is of greater degree is indicated by the accentuation of the pulmonic second sound and other manifestations of pulmonary engorgement.

The *pulmonary circulation time* is generally markedly prolonged, and is sometimes of great value in differentiating cardiac from bronchial asthma. The *cardiac output* is discussed on page 157. The roentgenogram of the chest, between attacks, generally shows severe pulmonary engorgement With pulmonary edema there may be intense clouding of the lung fields

Pulmonary Edema.—A decided majority of attacks of cardiac asthma, including some of great severity, run their course without discernible physical signs of pulmonary edema. This is especially true of those patients who have dozens of attacks of cardiac asthma over a long period Of course, this does not mean that lesser degrees of pulmonary edema, not disclosed by physical examination, are not present. But in other cases, signs of pulmonary edema may be elicited in the very first attack, or they may be detected only

after the patient has had a number of seizures Most often, the râles of pulmonary edema appear only after the attack has lasted for some time. But there are rare fulminant cases in which massive pulmonary edema with copious expectoration seems to develop almost as soon as the dyspnea. Some patients have a number of such attacks, each so terrifying that the physician thinks it will be the last. *Pulmonary edema is further discussed in Chapter XIV.*

Course of the Attack.—The duration of an attack of cardiac asthma varies within wide limits The average in 26 cases observed by Pratt was one hour. In the mildest attacks, the patient awakens with respiratory oppression, draws a few deep breaths and the episode is over. In other instances, there is agonizing dyspnea for hours. Rarely, a "status asthmaticus" develops, in which, with little relief from morphine or other agents, paroxysms of dyspnea follow close on one another for hours or even days

Although a well-marked paroxysm of cardiac asthma frightens the patient and gives the physician who is present many anxious moments, death during an attack is unusual. Of course, it is to be presumed that in the most severe bouts of cardiac asthma death occurs before the physician arrives Probably, some of the instances of death during sleep in hypertensive and arteriosclerotic subjects, in which pulmonary edema is found at necropsy, are of this variety. But there are patients who survive dozens of severe attacks, including a number with manifest pulmonary edema. Those cases in which the pulmonary edema is massive with abundant expectoration have a very serious prognosis, though even here recovery may occur on a number of occasions.

Following the spontaneous termination of an attack or its relief by morphine, the patient generally drops off to sleep. He may feel quite well the next morning or there may be exhaustion Following the initial attacks, if severe, the patients are usually badly frightened; the psychic response has much in common with that of angina pectoris. Individuals subject to nocturnal attacks may be afraid to go to sleep.

PATHOGENESIS OF PAROXYSMAL DYSPNEA

In the usual continuous and exertional dyspnea of heart failure, the shortness of breath is brought on by exertion and relieved by rest. Only in the most severe cases is it also present at rest, and then it is continuous. The dyspnea seems to be correlated with the oxygen consumption, appearing when the latter surpasses a threshold and disappearing when the oxidative metabolism falls below this level. Paroxysmal dyspnea, on the other hand, is not immediately incited by obvious physical exertion, in fact, it occurs most often when the metabolic demands on the circulation *seem* to be at a

minimum, namely, during the early hours of sleep. Moreover, the dyspnea often terminates spontaneously, *i. e.*, without any obvious decrease in the metabolic demands on the circulation. These facts indicate that factors enter into the pathogenesis of paroxysmal dyspnea which do not participate in the production of exertional dyspnea. Of course, this does not mean that there are not also pathogenetic factors common to both forms of cardiac dyspnea; actually, we shall see below that the underlying basis of both exertional and paroxysmal dyspnea is largely identical.

The Occurrence of Cardiac Asthma.—Fundamental for the study of the pathogenesis of paroxysmal dyspnea is the fact that *it occurs almost exclusively in conditions characterized by failure of the left ventricle.* (For statistics, see Palmer and White.[13]) Cardiac asthma is most common in hypertension and arteriosclerotic heart disease Severe and classical attacks are seen in the hypertension of glomerulonephritis, especially in the acute stage. Other frequent causes are syphilis aortitis with aortic regurgitation or narrowing of the mouths of the coronary arteries and rheumatic aortic regurgitation and stenosis. In mitral disease, on the other hand, typical cardiac asthma is very uncommon, most of the episodes of acute pulmonary congestion in mitral stenosis observed by McGinn and White[12] were incited by unusual exertion or paroxysmal tachycardia. The majority of the unusual instances of mitral disease with true cardiac asthma are those in which insufficiency of the valve predominates and the left ventricle is enlarged, so that it is readily conceivable that failure of the left ventricle is concerned even in these cases of mitral disease. In predominant mitral stenosis with a small left ventricle, cardiac asthma is decidedly rare, perhaps least rare in pregnancy (page 691). Paroxysmal dyspnea is also very rare in failure of the right heart secondary to emphysema and other pulmonary diseases, as well as kyphoscoliosis. Cardiac asthma also seems to be a rarity, if it occurs at all in typical form, in heart failure due to thyroid disease and mediastino-pericarditis; it was absent in all 26 cases of thyroid heart mentioned by Palmer and White.

The Rôle of Pulmonary Engorgement in Cardiac Asthma.—In the preceding section, we have seen that cardiac asthma occurs almost exclusively in conditions in which the left ventricle is strained. This occurrence led even the earliest investigators to the conception that cardiac asthma is the result of pulmonary engorgement. In his initial description of this form of air hunger, Hope thought it due to "an excess of blood in the lungs compressing the air vessels, and preventing the free admission of air; also sometimes causing its own retardation." Later, this view was formulated more precisely by Traube (page 122), who considered the shortness of breath a consequence of failure of the left ventricle with resultant pul-

monary stasis. Since the experiments of Welch on the production of pulmonary edema (page 220), this view has been widely accepted. The conception is that if the contractile power of the left ventricle is severely impaired while the right ventricle functions more efficiently engorgement of the pulmonary circuit must occur, and evidence has already been summarized in the preceding chapter that such congestion of the lungs produces dyspnea.

There is no doubt that intense pulmonary engorgement is present in at least the vast majority, if not all, attacks of cardiac asthma. The pulmonic second sound is accentuated, most often strikingly. The arm-to-tongue circulation time is almost always markedly prolonged, which, in view of the frequently normal venous pressure, is to be attributed to slowing of blood flow through the lungs. Weiss and Robb[19] found that the velocity of pulmonary blood flow is regularly slower during the attack than is the speed between the seizures. They found evidence that the blood content of the lungs is increased in patients with cardiac asthma. As a rule, the roentgenogram of individuals with cardiac asthma, taken between attacks, shows definitely the engorgement of the lungs. During the attack the engorgement may be accentuated and the lung fields clouded by pulmonary edema. The frequent development of pulmonary edema is, of course, in excellent harmony with the conception that there is acute engorgement and hypertension of the lesser circulation in cardiac asthma. The same is true of the not uncommon bloody expectoration of these patients.

Some of the most important evidence of the fundamental significance of pulmonary engorgement in the pathogenesis of at least many instances of cardiac asthma is afforded by the clinical course. One often observes that previously severe and frequent attacks of cardiac asthma disappear when the right heart fails, as shown by the development of swelling of the veins and liver and peripheral edema. This is often so striking that patients volunteer the information that when their legs became swollen, the nocturnal asthmatic paroxysms disappeared. I have also seen the reverse sequence, namely, the reappearance of cardiac asthma when evidences of right heart failure cleared up.

The predominant rôle of disturbances in the lesser circulation in the pathogenesis of cardiac asthma has been brought out with especial clarity in the detailed studies of Weiss and Robb. They find that in many patients with cardiac asthma the systemic circulation is hardly impaired, as shown by normal cardiac output, arteriovenous oxygen difference, and venous pressure; the arterial pressure may even be elevated. On the other hand, they found invariably conclusive evidences of passive engorgement of the pulmonary circuit, namely, increase in the blood content of the lungs, slowing of blood flow through the lungs, hypertension of the lesser

circulation, and decrease in vital capacity. Furthermore, all of these as well as the clinical manifestations of pulmonary engorgement mentioned above are greatly intensified during the actual attack. And in some of the attacks the engorgement of the pulmonary circuit becomes so intense that edema of the lungs results.

In the light of these facts, it would seem to be established that *cardiac asthma develops on the terrain of pulmonary engorgement and the actual paroxysm accompanies an intensification of the engorgement* Fundamentally, then, both the exertional and the paroxysmal dyspnea of left heart failure are of similar pathogenesis, for both result primarily from passive congestion of the lungs

The Exciting Causes of the Paroxysm.—Other questions immediately arise. What causes the exaggeration of the pulmonary engorgement which produces the dyspneic paroxysm soon after the patient has fallen asleep, just when the metabolic demands on the circulation seem to be least? Several mechanisms have been considered responsible

The Recumbent Posture —In many patients with cardiac asthma, the attacks do not occur if they are able to sleep propped up high in bed Many of them discover this means of relief for themselves. Further, the information is sometimes volunteered that if the patient slides down in bed while asleep, a paroxysm ensues. Merely sitting up in bed relieves many attacks of cardiac asthma The remarkable feature is that some who suffer from violent attacks of nocturnal dyspnea are able to walk considerable distances without discomfort. Indeed, when awakened by dyspnea they often walk about the bedroom to aid in obtaining relief

The above clinical observations would indicate that many seizures of cardiac asthma are essentially manifestations of orthopnea. In Chapter X, it will be seen that the orthopnea of left-sided failure is largely due to pulmonary engorgement resulting from a change in the distribution of the blood, with the assumption of the recumbent posture, blood is displaced from the splanchnic area and lower extremities to the pulmonary circuit. The patient with cardiac asthma has pulmonary engorgement even when awake and in the erect posture When he falls asleep in the recumbent posture, especially if he slides down in bed, blood is displaced from the infradiaphragmatic vessels to the pulmonary circuit, the pulmonary engorgement is intensified, and the resultant decrease in vital capacity and increase in ventilation finally becomes so pronounced that the consequent dyspnea awakens the patient.

However, the assumption of the recumbent posture does not completely explain all instances of cardiac asthma. For many of the patients do not become dyspneic when recumbent if they remain awake, but are roused by shortness of breath some time after they

fall asleep even though they do not slide down. Here, there must be other pathogenetic factors resulting from sleep.

Sleep.—The great importance of sleep is shown by the fact that many victims of cardiac asthma are afraid to go to sleep, for they know that they will be awakened by a paroxysm. It is possible that the diminution in the irritability of the central nervous system during sleep is concerned in the liability of individuals with left ventricular failure to develop paroxysms of cardiac asthma when asleep. The lessened sensitivity may allow pulmonary engorgement, resulting from the assumption of the recumbent position in the presence of left ventricular weakness, to attain a much higher degree before reflexly inciting an increase in ventilation (page 125) than is the case when awake The result is that the patient does not awake until the lungs become intensely engorged, perhaps to the degree of producing pulmonary edema But while such a rôle of decreased sensitivity of the nervous system during sleep seems probable, it is not yet proved.

Periodic Breathing.—Not rarely, the respiration of cardiac patients becomes periodic when they fall asleep (page 160) The possibility that at least some attacks of cardiac asthma are inaugurated by the dyspneic phase of such periodic breathing was entertained by Traube[15] and Mackenzie [11] This mechanism apparently occurs in some of the cases, but they represent only a small fraction of the totality of those with cardiac asthma.

Dreams.—Sufferers from cardiac asthma often state that the paroxysm awakens them from a dream, and some clinicians have thought that dreams may precipitate the attack. It seems plausible that fear or other emotion accompanying a nightmare may increase the venous return to the heart and thus promote pulmonary engorgement in the presence of a weak left ventricle Moreover, MacWilliam[10] found that during dreams both the systolic and diastolic arterial pressures may rise, the former as much as 70 mm. Hg. Such a rise in arterial pressure may well precipitate pulmonary engorgement in an individual with a weak left ventricle That sudden fear increases ventilation has been shown by Harrison. But it should be borne in mind that unpleasant dreams are a very common symptom in circulatory failure, whether or not there are nocturnal paroxysms of dyspnea.

Resorption of Edema—Volhard[16] and Brunn[2] have advanced the theory that nocturnal attacks of cardiac asthma result from the resorption of edema fluid into the blood stream when the patient assumes the horizontal posture at night It is true that most individuals with cardiac asthma have no demonstrable edema, but there may be considerable water retention in the tissues without pitting swelling. Volhard's theory is that the resorption of the edema fluid increases the blood volume and thus the work of the

heart The right heart is able to master the increased load but the weakened left ventricle is not, with the result that pulmonary engorgement and dyspnea develop In favor of this theory, Volhard adduces the excellent therapeutic results he has obtained in cardiac asthma with a dry diet and the unfavorable influence of the ingestion of large amounts of fluid I have also often seen striking therapeutic results in cardiac asthma with rigid fluid restriction. Dehydration with mercurial diuretics also sometimes prevents the recurrence of cardiac asthma But in other cases these measures fail.

In the frequent cases in which fluid is absorbed from the tissues at night, as shown by nycturia and the clearing up of minimal edema, it would seem probable that the entrance of the fluid into the blood stream increases the work of the heart. Whether the mobilization of fluid is often of sufficient quantitative import seriously to embarrass the heart is another question. Harrison[5] found the oxygen capacity of the blood usually higher in the morning than the evening, which would speak against significant increase in blood volume as a result of resorption of fluid. Moreover, nocturnal cardiac asthma is common in patients who are in bed during the day, and in whom there would seem to be no reason to presuppose greatly accelerated mobilization of fluid after the patient falls asleep But in individuals who are up and about during the day, nocturnal resportion of fluid may sometimes be an accessory factor in overloading the heart at night

Cough.—Harrison believes that some attacks of cardiac asthma are precipitated by cough Because of the decreased nervous irritability during sleep, the increased bronchial secretion often present in pulmonary engorgement accumulates until it produces a violent paroxysm of cough, which produces dyspnea through several mechanisms analyzed in detail by Harrison Actually, cough is a prominent feature in some attacks of cardiac asthma, and may well precipitate some attacks. But in other cases, cough is a result of the paroxysm, induced by the presence of edema fluid in the bronchi

Reflex Factors —Wassermann[18] observed relief of cardiac asthma by section of the "depressor" nerves, and amelioration of attacks by carotid sinus pressure. On the basis of these and other observations, he believes that some forms of paroxysmal dyspnea are initiated by reflexes from the root of the aorta. In three instances of cardiac asthma, Weiss and Robb[19] "blocked the vagus nerve with procaine hydrochloride, which resulted in improvement of the dyspnea, orthopnea, elevation of the vital capacity, and ipsilateral disappearance of rhonchi and râles, and improvement of the breath sounds." The study of reflex factors in cardiac asthma would appear to offer a fruitful field, but little is known as yet.

Cerebral Factors.—Fraser[4] and others have thought that the paroxysmal dyspnea of left ventricular failure is due to diminished

blood flow through the respiratory center. This theory would appear to be disproved by the finding of Weiss and Robb that the cardiac output may be normal in cardiac asthma, and by the observation of Harrison that the arteriovenous gas differences between the arteries and the internal jugular vein are normal in this condition.

Ischemia of the respiratory center due to *cerebral arteriosclerosis* and *cerebral angiospasms* has also been considered as the basis of some attacks of paroxysmal dyspnea, especially in hypertensive individuals According to Volhard,[17] such attacks of "cerebral asthma" are apt to be associated with other focal cerebral symptoms and with periodic breathing, do not lead to pulmonary edema, and do not necessarily develop in the recumbent posture But he admits that the differentiation from true cardiac asthma is often difficult, and it seems probable that "cerebral asthma" is a rarity, if it occurs at all.

Eppinger's Theory of Hypercirculation.—In the foregoing, it has been seen that most attacks of cardiac asthma are probably precipitated by factors which increase the venous return to the heart This conception is largely due to the studies of Eppinger, von Papp and Schwarz[3] Their investigations originated in the observation in patients with cardiac asthma that when the superficial veins on the back of the hand were emptied by striking, they refilled very rapidly They considered this an indication of acceleration of the circulation Eppinger and his associates then found that in many instances of cardiac asthma, the cardiac output increases during the day, to reach an abnormally high level during the evening hours They also found that morphine, the sovereign remedy for cardiac asthma, decreases the cardiac output On the basis of these and other observations, Eppinger believes that paroxysms of cardiac asthma result from increased venous return to the heart, which the weakened left ventricle is unable to handle adequately, with resultant pulmonary engorgement and dyspnea. He considers that the functional capacity of the already weak left ventricle is further decreased at night because of a hypothetical decrease in tone due to vagal predominance during sleep Eppinger and his associates attribute the increased venous return to peripheral vasodilatation, allowing the blood to pass more readily from the arteries to the veins They believe a variety of causes responsible for the vasodilatation and circulatory acceleration, including impairment of the buffering power of the tissues by overproduction of lactic acid and nocturnal retention of carbon dioxide They also consider it probable that psychic factors, including dreams, sometimes play a part in accelerating the circulation

Eppinger's work rendered a service by calling attention to increase in venous return as a precipitating factor of cardiac asthma But the contention that the cardiac output may be increased above the normal in cardiac asthma has not been substantiated, and would seem to be based on observations with inaccurate technic Using the most accurate method available, that of direct puncture of the right auricle (page 35), Lauter[9] found the cardiac output decreased in a patient with cardiac asthma Weiss and Robb[19] found the cardiac output during the attack either unchanged or decreased, never increased. Eppinger's conception of peripheral vasodilatation in cardiac asthma seems purely hypothetical

Summary.—Much remains to be learned regarding the causation of cardiac asthma. The following perhaps summarizes present knowledge: Cardiac asthma is almost always a symptom of left ventricular failure. Like the exertional dyspnea of left-sided heart failure, cardiac asthma is a manifestation of pulmonary engorgement The actual paroxysm is precipitated by intensification of pulmonary engorgement, which may become so marked as to produce pulmonary edema What is largely obscure is the cause of the increase in pulmonary engorgement that brings on the attack. The combination of the recumbent position and sleep appear to be of fundamental importance With a weakened left ventricle, the recumbent position predisposes to pulmonary engorgement because it entails a shift of blood from the abdomen and lower extremities to the lungs And the diminished sensitivity of the nervous system during sleep perhaps allows this engorgement to attain a higher degree than would otherwise occur. Among the other factors which may participate in the nocturnal intensification of pulmonary engorgement are dreams, cough, and the resorption of manifest or occult edema when recumbent.

Why nocturnal paroxysms of cardiac asthma are so much rarer in the pulmonary engorgement of mitral stenosis than in that of left ventricular failure remains to be explained.

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CHAPTER IX

PERIODIC BREATHING

THE spectacular phenomenon of periodic breathing was first brought to the general attention of the profession by the observations of the Dublin clinicians, Cheyne[4] and Stokes,[28]* on patients whom they considered to suffer from fatty degeneration of the heart. Since then, Cheyne-Stokes breathing has been used by many as a generic term for periodic respiration. Others restrict the term to the type of periodic respiration described by the Irish clinicians, in which the period of respiratory activity is marked by gradual waxing and waning of the depth of the individual respirations The term Biot[2] breathing is used for the variety of periodic breathing, encountered especially in meningitis and other intracranial disease, in which the individual breaths are of about the same depth, the respiratory periods starting and ending abruptly. But the distinction is in no way fundamental and there are many intermediary forms

OCCURRENCE OF PERIODIC BREATHING

Despite the ominous prognostic significance justly attributed to Cheyne-Stokes breathing in disease, it occurs under a variety of circumstances in health Occasionally, there is distinct periodicity of respiration during sleep which, especially in the very young and the very old, is sometimes marked enough to warrant the term Cheyne-Stokes breathing During the hibernation of the Myoxus and other forms, periodic breathing is present (Mosso[19]) It is not uncommon at high altitudes, particularly after slight exertion and during sleep, and was long ago described by Mosso as an outstanding symptom of mountain sickness The apnea which follows hyperventilation may be succeeded by Cheyne-Stokes breathing

Concerning the occurrence of periodic breathing in disease, Cheyne and Stokes thought it characteristic of fatty degeneration

* Periodic breathing had previously been observed by John Hunter and by Nicholas,[11] a physician of Grenoble Nicholas, in 1786, described the breathing of a sick officer of eighty-one years as follows "But what indeed more extraordinary than *this irregularity (of the pulse) was an absolute suspension, a cessation of the* movements of the lung for twenty-five or thirty seconds, at each thirty-fifth or thirty-sixth respiration, then the play of the organ was reëstablished little by little, and by a very evident gradation it resumed its ordinary energy, to stop again almost at the indicated instant" Gibson[11] considers it likely that the following sentence from the Hippocratic First Book of the Epidemics refers to Cheyne-Stokes breathing "The respiration throughout, like that of a person recollecting himself, was infrequent and deep" The interpretation seems dubious to me A splendid historical survey of Cheyne-Stokes breathing is given by Gibson

of the heart, but it may occur in practically all varieties of cardiac insufficiency. The most common cause is failure of the arteriosclerotic heart, especially when this is associated with hypertension, cerebral arteriosclerosis, or uremia. Cheyne-Stokes breathing has seemed to me decidedly more common when the cardiac insufficiency involves primarily the left ventricle, as in hypertensive, coronary, and aortic disease, than in circulatory failure secondary to mitral stenosis or pulmonary disease On the rare occasions that Cheyne-Stokes breathing occurs in such acute infections as pneumonia or typhoid fever, other evidences of circulatory failure are also present.

The other great class of diseases in which periodic breathing occurs involve the brain, particularly with increased intracranial pressure Among these conditions are cerebral hemorrhage and thrombosis, tuberculous and other forms of meningitis, brain tumors (especially of the brain stem), hydrocephalus, intracranial aneurysms, edema of the brain, general paresis and other forms of syphilitic brain disease, and acute and chronic encephalitides.

Finally, Cheyne-Stokes breathing may result from the administration of narcotics Of these, by far the most important, as first observed by Traube,[29] is morphine, this is so common a cause of periodic breathing, especially in arteriosclerotic individuals, that on observing the phenomenon I always ask immediately whether morphine has been administered Alcohol, barbital derivatives, and other hypnotics may also induce Cheyne-Stokes breathing, particularly when cerebral arteriosclerosis is present.

In the various states in which Cheyne-Stokes breathing occurs, the phenomenon is often present only when the patient is asleep, to disappear on awakening Harrison[14] has pointed out that Cheyne-Stokes breathing is especially closely connected with the state when falling asleep, and may disappear when sleep becomes deep.

Experimentally, Cheyne-Stokes breathing was first produced by Schiff,[26] who observed in animal experiments that pressure on the medulla oblongata results in the typical waxing and waning respiration. Since then, Cheyne-Stokes respiration has been produced by a variety of means, including the administration of morphine and other narcotics and various procedures resulting in cerebral anoxemia; this will be considered further in connection with the pathogenesis.

CLINICAL PICTURE OF PERIODIC BREATHING

The Respiration.—The original description of Cheyne is classical: "For several days his breathing was irregular; it would entirely cease for a quarter of a minute, then it would become perceptible,

though very low, then by degrees it would become heaving and quick, and then it would gradually cease again: this revolution in the state of his breathing occupied about a minute, during which there were about thirty acts of respiration"

In typical Cheyne-Stokes breathing, the spacing of the successive respiratory phases is generally quite rhythmic; the length of the individual periods of apnea is almost if not perfectly equal and the same is true of the periods of respiratory activity During the crescendo phase of the latter, the breathing accelerates as it becomes progressively deeper, the reverse is true in the diminuendo phase. During the apneic period, no movement of the chest is discernible and, as the original observers noted, the patient may appear dead until breathing starts again. The lengths of the respiratory and apneic periods vary greatly, the former being usually somewhat longer In 12 cases, Sansom[25] found apnea to last between ten and forty seconds, respiration between fifteen and fifty-five seconds. He quotes a case in which each period occupied two minutes, and I have seen apneic periods of about seventy-five seconds the evening before death. With long apneic periods, cyanosis may deepen strikingly toward the end of each respiratory standstill This may be accompanied by muscular twitchings, especially in the face.

In other instances of periodic breathing, the respiratory periods occur at entirely irregular intervals. They may be of varying length and there are no regular ascending and descending phases as in typical Cheyne-Stokes breathing This type of periodic respiration was originally described by Biot,[2] after whom it is called, as occurring in meningitis, but is also seen on rare occasions in other conditions.

Occasionally, there is an abortive movement of the chest in the midst of apnea. At the height of dyspnea, the breathing may be very laborious, the patient calling into play the accessory muscles of respiration, grasping the side of the bed, and attempting to lift his head. In other cases, even though the sensorium is unimpaired, the deep breaths are drawn without evident distress, *i e*, there is hyperpnea but not dyspnea In a description of Cheyne-Stokes breathing from which he suffered, Vogl[31] states that he was unable voluntarily to draw a deep breath during the apneic period, but I have several times induced patients to draw breaths during this period.

Circulatory Periodicity in Cheyne-Stokes Breathing.—Periodic changes in the circulation correlated with the phases of Cheyne-Stokes breathing have been extensively studied, largely in the effort to elucidate the periodicity of respiration Sometimes, little change in blood pressure or heart rate can be detected by the usual

clinical methods But in other instances rhythmic alternations in blood pressure and pulse rate are pronounced.

In clinical cases of Cheyne-Stokes breathing due to increased intracranial pressure, as in the experimental forms (page 168), the studies of Cushing[6] and Eyster[10] have shown that the blood pressure rises and the pulse rate slows during respiration and the reverse occurs during apnea.

When the periodic breathing results from cardiac, arterial, or hypertensive disease, or morphine intoxication, the relations between respiratory activity and blood pressure are different and not so simple. In 8 cases of cardiac and arterial disease with Cheyne-Stokes breathing, Eyster found that the blood pressure rose during apnea and fell during respiration, *i. e.*, the reverse of what occurs in increased intracranial tension. The observations of Clark and Hamill[5] were somewhat different. In a patient with morphine poisoning, 2 with arteriosclerotic heart disease, and 1 with a cerebral vascular accident, they found the most striking change in blood pressure to be a fall in the last half of or throughout apnea with a rise during respiration which was sometimes prolonged into the first part of apnea In an instance of morphine poisoning studied by Edens,[9] the systolic pressure was only 40 mm. at the beginning of apnea, rose to 180 mm in the middle of apnea, to sink again to 40 mm at the beginning of respiration. In several cases observed by the writer, there was no constant change in the arterial pressure, though more often it fell toward the end of protracted apnea. It would appear that factors having opposite effects on the blood pressure come into play during Cheyne-Stokes breathing. On the one hand, diminution in the venous return to the heart as a result of the respiratory standstill and asphyctic weakening of the heart tend to lower the arterial pressure as apnea lasts; it is presumably these factors which result in the elevation in venous pressure during apnea described by Meyer and Middleton.[17] On the other hand, the asphyxia during apnea produces vasoconstriction and thus tends to elevate the arterial pressure The resultant of these opposing factors may vary in different cases. (See also page 168.)

Interesting observations on periodic changes in heart rhythm in a patient with Cheyne-Stokes respiration were made by Resnik and Lathrop.[23] Toward the end of each apneic period, there appeared "displacement of the pacemaker to the auriculo-ventricular node and the bundle branches of the main stem of the conduction system; depression of auriculo-ventricular conduction and conspicuous slowing of impulse formation at the sino-auricular node." That these changes were due to vagal stimulation was shown by their abolition by atropine.

Nervous and Ocular Accompaniments of Cheyne-Stokes Breathing.—Periodic respiration, of course, often occurs in comatose patients, while in other cases consciousness is preserved at all times An interesting and not uncommon phenomenon is for consciousness to be lost during apnea, to reawaken with each period of respiratory activity, the patient opening his eyes and even conversing with bystanders

Leube[15] long ago described rhythmic changes in the pupils during Cheyne-Stokes respiration, contraction during apnea and dilatation in hyperpnea. But in many cases there is no appreciable change in the size of the pupils. The pupillary fluctuation, when present, is probably an exaggeration of the slight fluctuation which has been observed to accompany the drawing of a deep breath even in health and particularly in comatose patients with continuous hyperpnea. Conjugate deviation and nystagmus have been observed to accompany the pupillary contraction Not uncommonly, the eyelids are shut in apnea and open in hyperpnea Rhythmic fluctuations in the caliber of the retinal vessels with contraction during apnea have been noted in some cases but not in others

DURATION AND PROGNOSTIC SIGNIFICANCE OF PERIODIC BREATHING

Slight waxing and waning of respiration during sleep, especially in the very young and the very old, is of little significance Diametrically the opposite holds for true Cheyne-Stokes breathing with notable periods of complete apnea, it has long been regarded as a harbinger of death, and indeed in most instances does indicate that the end is not far distant But there are also circumstances in which recovery follows a period of Cheyne-Stokes breathing. This occurs on rare occasions in pneumonia and other acute infections. I have seen recovery in a patient with periodic breathing of the Biot type in meningococcus meningitis In brain tumors and other intracranial lesions, decompression may be followed by resumption of regular respiration, I have seen this follow lumbar puncture in the malignant phase of essential hypertension where the cerebrospinal pressure was very high. In periodic breathing due to cerebral hemorrhage or thrombosis, survival of the acute episode is not a great rarity, although the respiratory periodicity is decidedly a grave prognostic indication

In the hypertensive individuals with coronary and cerebral arteriosclerosis who constitute the great contingent of cases with Cheyne-Stokes breathing, the outlook is very grave. But even here there are cases in which the course is protracted and even some in which sufficient improvement for the patient to leave bed occurs. Thus, I recently saw a patient with hypertension and coronary

and cerebral arteriosclerosis in whom Cheyne-Stokes breathing was present almost continuously for six weeks, which cleared up after an intravenous injection of aminophyllin, and who left the hospital on foot. Sansom[28] mentions cases in the aged in which Cheyne-Stokes breathing was present for months, including one in a gentleman, aged ninety-two years, who had had the sign for many years, although he was otherwise quite well. It is often possible to render the breathing regular for at least a time by therapeutic measures (page 785).

PATHOGENESIS OF CHEYNE-STOKES BREATHING

The first noteworthy theory of the mechanism of Cheyne-Stokes breathing was advanced by Traube.[29] He observed that the phenomenon occurs in two groups of cases, namely, those with an intracranial lesion in the presence of an intact heart, and those with cardiac disease but no change in the contents of the skull. He reasoned that the pathogenetic factor common to these two seemingly dissociated states is a diminished supply of arterialized blood to the brain. Traube was of the opinion that this decrease in the arterial irrigation of the brain produced periodic breathing through the intermediacy of diminution in the irritability of the respiratory center as a result of oxygen deficiency. In support of this view, he adduced his observation that morphine often brings out Cheyne-Stokes breathing in either of the above classes of cases. As a result of the diminished irritability of the respiratory center, there is apnea until a high concentration of carbon dioxide accumulates in the blood. The accumulated carbon dioxide stimulates the vagal and other nerve endings and thus initiates respiration. The resultant deep breathing again depletes the carbon dioxide of the blood so that there is another period of apnea, and the cycle is repeated.

Closer consideration of Traube's theory shows that it contains no actual explanation of why cerebral oxygen deficiency results in periodic breathing and not merely continuous hyperpnea. Nevertheless, he discerned three of the pathogenetic factors which have since dominated the search for the mechanism of Cheyne-Stokes breathing: cerebral oxygen want, deficiency of carbon dioxide in the arterial blood, and diminution in the sensitivity of the respiratory center. In the following, we shall consider these factors individually.

Oxygen Deficiency.—There is good evidence that oxygen deficiency is concerned in the genesis of at least some forms of Cheyne-Stokes breathing. It was mentioned above that periodic breathing is common during residence at high altitudes, and that it occurs in mountain sickness.

Douglas and Haldane[8] produced Cheyne-Stokes breathing by two procedures in which anoxemia occurs. The first was by means of voluntary hyperventilation. They observed that in many individuals the apnea which follows protracted hyperventilation is in turn succeeded by several cycles of periodic breathing The course of events in this experiment would seem to be as follows: Hyperventilation diminishes the carbon dioxide content of the arterial blood to a level far below the threshold for stimulation of the respiratory center. The result is apnea During the apnea, the oxygen of the blood is depleted and carbon dioxide accumulates. But before the carbon dioxide content of the arterial blood reaches the threshold for stimulation of the respiratory center, anoxemia becomes sufficiently marked to initiate breathing. The ensuing respiration relieves the anoxemia but at the same time enough carbon dioxide is blown off again to produce apnea, so that the cycle is repeated. The reason that the periodic breathing does not continue indefinitely is that with each apneic period the carbon dioxide pressure in the blood reaches a higher level, until after several cycles it surpasses the threshold for stimulation of the respiratory center and breathing becomes continuous Evidence that the oxygen deficiency actually produces the periodic breathing in this experiment is afforded by Douglas and Haldane's further observation that if the initial hyperventilation is carried out in an atmosphere of high oxygen concentration instead of air, the ensuing apnea is greatly prolonged but is succeeded by regular and not by periodic breathing. Douglas and Haldane also induced periodic breathing by having the subject breathe through a long tube containing soda lime to absorb carbon dioxide, a procedure which likewise produces anoxemia and carbon dioxide deficiency.

The periodic breathing following hyperventilation would thus seem to be an expression of the transference of the "lead" in the chemical regulation of respiration from the carbon dioxide to the oxygen coefficient The appearance of periodic breathing under these circumstances is further interpreted by Haldane[13] as follows. Under the usual circumstances of life, chemical regulation of respiration is effected primarily through the carbon dioxide of the blood But, despite its great sensitivity to shifts in the partial pressure of carbon dioxide in the blood, the respiratory center reacts somewhat slowly to such changes, it may be said to have a certain "inertia." This inertia is due to the fact that the tissues have various buffering mechanisms and an appreciable capacity for storing carbon dioxide, so that some time elapses before changes in the level of the carbon dioxide of the blood are transmitted to the tissues of the respiratory center and thus affect breathing. This is a very useful adaptation, for it prevents sudden changes in respiration during physical exercise, speaking, etc Haldane draws

an analogy between the function of carbon dioxide in keeping respiration "smooth" and the similar action of the flywheel of a steam engine. But conditions are different if oxygen deficiency becomes so pronounced as to stimulate respiration The tissues are believed to have little storage capacity for oxygen, so that hyperpnea is quickly induced, respiration becomes jerky and, in Haldane's analogy, like the action of a steam engine without a flywheel.

Further support for the conception that oxygen deficiency plays a part in the production of clinical Cheyne-Stokes breathing was afforded by the observation of Pembrey and Allen[22] that the respiration is rendered continuous by the inhalation of high concentrations of oxygen However, subsequent observers have found that this is not always the case While Uhlenbruck[30] also relieved Cheyne-Stokes breathing by the administration of oxygen, he found that the effect wore off and the periodicity returned despite continuance of the oxygen therapy. Dautrebande and Regnier,[7] Anthony, Cohn and Steele,[1] and Harrison[14] also observed Cheyne-Stokes breathing in which oxygen therapy did not completely abolish the periodicity. But even in these cases, apnea is usually prolonged and the respiratory phase quieter. Oxygen has had little effect in several cases of my observation, but on two occasions I have observed quick return to continuous respiration which lasted for the several hours which the patients were kept in the tent.

Analyses of the arterial blood show that whatever the rôle of cerebral oxygen deficiency in the production of Cheyne-Stokes breathing, it is not always due to arterial anoxemia. While the oxygen saturation of the arterial blood falls during apnea and rises during respiration (Anthony, Cohn and Steele[1]), cases have been observed (*e. g.*, by Resnik and Lathrop[23]) in which it is always within normal limits. Studying the average composition of arterial blood throughout a respiratory cycle, Harrison and Wilkins[14] found anoxemia in 11 of 18 patients, and oxygen saturation above 90 per cent in the remainder; the saturation was above 93 per cent in 4 cases and was therefore entirely normal In the cases with such high arterial oxygen saturation, it is not surprising that the inhalation of oxygen has little effect on the periodicity of the breathing even though cerebral oxygen deficiency is concerned in its production

Clinical observation shows that oxygen deficiency *per se* does not suffice to cause Cheyne-Stokes breathing. For patients with right ventricular failure secondary to pulmonary lesions and those with congenital heart disease, who may be deeply cyanotic for years, rarely develop periodic respiration. It is thus evident that oxygen deficiency calls forth Cheyne-Stokes breathing only under certain conditions and in associations with other factors.

Carbon Dioxide Deficiency.—Depression of the carbon dioxide tension of the arterial blood favors the development of Cheyne-Stokes breathing. In the experimental periodic breathing produced by Douglas and Haldane[8] by hyperventilation, carbon dioxide deficiency is concerned (page 165). Of 18 patients with Cheyne-Stokes breathing studied by Harrison and Wilkins,[14] the carbon *dioxide tension in the arterial blood was below normal in 13, within* the normal range in 3, and above normal in 2, one of the latter was moribund and the other was sleeping when the blood was drawn. But the most important evidence indicating the relation of the carbon dioxide tension of the blood to Cheyne-Stokes breathing was obtained by Pembrey and Allen,[22] who showed that the inhalation of carbon dioxide renders the respiration regular. This has been confirmed by Anthony, Cohn and Steele[1] and others, and I have repeatedly observed it. However, low carbon dioxide pressure in the arterial blood is not a necessary condition for the occurrence of Cheyne-Stokes breathing Thus, in morphine poisoning respiration may be periodic despite very high carbon dioxide pressure in the arterial blood. But even when the carbon dioxide tension of the blood is not depressed, inhalation of the gas abolishes the periodicity of the breathing, showing that the occurrence of the latter is conditioned by a carbon dioxide pressure which is *relatively* low in comparison to other factors in the regulation of respiration, notably the sensitivity of the respiratory center.

The Reaction of the Blood.—Hyperventilation may depress the carbon dioxide and consequently the hydrogen-ion concentration of the arterial blood below the normal. Such was the case in 9 of Harrison's 18 patients with Cheyne-Stokes breathing Several investigators have considered the possibility that depression of hydrogen-ion concentration, through the inhibitory effect on the dissociation of oxyhemoglobin, may intensify oxygen want in the tissues, and thus be concerned in the genesis of Cheyne-Stokes breathing.

Diminished Irritability of the Respiratory Center.—This factor is of primary importance in the genesis of some forms of Cheyne-Stokes breathing. It was mentioned above that Cheyne-Stokes respiration can be produced experimentally by the administration of morphine. And patients with conditions predisposing to Cheyne-Stokes breathing (*e. g*, arteriosclerotic heart disease with left ventricular failure) are often thrown into periodic respiration by morphine. Cheyne-Stokes breathing often occurs during sleep in individuals who breathe regularly when awake, and is said to be the rule in hibernating animals. It would seem that both sleep and morphine lead to Cheyne-Stokes breathing by depressing the irritability of the respiratory center This conception is in good accord with the fact that in Cheyne-Stokes breathing evoked by

morphine, and sometimes by sleep, the carbon dioxide tension of the blood is elevated, a factor which ordinarily militates against periodic breathing. The mechanism by which morphine leads to Cheyne-Stokes breathing may well be similar to that of periodic respiration due to hyperventilation For the depression of the respiratory center so diminishes ventilation that anoxemia results. And it is to be presumed that the depression of the respiratory center includes elevation of its threshold for carbon dioxide, which comes to the same as decrease in the carbon dioxide tension in the blood due to hyperventilation. The result is that the "lead" in the chemical regulation of respiration is transferred from carbon dioxide to oxygen, and periodic respiration is produced in the fashion described on page 165.

Increased Intracranial Pressure.—The experimental investigations of Leyden,[16] Naunyn and Schreiber,[20] and especially Cushing[9] and Eyster[10] demonstrated long ago that the rhythmic undulations of blood pressure resulting from increased intracranial tension are accompanied by synchronous respiratory waves In these cases, blood pressure rises during respiratory activity and falls during apnea Eyster found that the periodicity of respiration in experimentally increased intracranial tension is present only as long as the rhythmic variations in blood pressure persist. The blood pressure alternately rises and falls below the level of the intracranial tension and is paralleled by the respiration and heart rate.

The parallel oscillation of respiratory activity and of blood pressure above and below the height of the intracranial tension indicate that the mechanism of Cheyne-Stokes breathing in cases with great elevation of intracranial pressure is as follows: When the intracranial tension reaches a level above the arterial pressure, the blood supply to the medullary centers is cut off. While up to a certain limit curtailment of blood flow through the respiratory center stimulates it, more severe ischemia results in depression of respiration, presumably as a result of oxygen want (Schmidt[27]). This apparently is the manner in which apnea is produced by increased intracranial pressure. The vasomotor center, on the other hand, responds by inducing a rise in arterial pressure, Eyster[10] found that it is not nearly so susceptible to ischemia as is the respiratory center and often responds when in a condition of complete ischemia. The resultant rise in blood pressure above the intracranial tension relieves the ischemia of the respiratory center so that breathing starts. But the ischemic stimulus to the vasomotor center is then eliminated, with the result that the blood pressure drops, the respiratory center again ceases its function, and a new cycle is initiated. In other words, the respiratory periodicity of increased intracranial pressure is secondary to circulatory periodicity.

The mechanism of Cheyne-Stokes breathing in brain tumors, cerebral hemorrhage, fractures of the skull, and other conditions with very greatly increased intracranial pressure thus seems quite clear. The question arises whether increased intracranial pressure does not play a part in the causation of some instances of Cheyne-Stokes breathing due to heart failure and hypertension. Elevation of venous pressure due to right heart failure is always accompanied by corresponding increase in cerebrospinal pressure. When essential hypertension enters the malignant phase with the development of papilledema, the intracranial pressure is elevated, I have repeatedly found the pressure of the cerebrospinal fluid in such patients above 300 mm. of water in the absence of heart failure On several occasions, I have observed in these patients Cheyne-Stokes breathing which could not be attributed to heart failure Indeed, the entire clinical picture sometimes simulates that of brain tumor. Elevation of the pressure of the cerebrospinal fluid in individuals with Cheyne-Stokes breathing has been reported by Moeller[18] and others Moeller found that the elevated pressure was higher during respiratory activity and lower during apnea. Uhlenbruck[30] and Carnot, Caroli and Freher[3] have shown that the periodicity of the respiration in such cases can sometimes be abolished by lumbar puncture, I have made a similar observation

In view of these findings, it would seem that elevation of intracranial pressure is sometimes a significant factor in the genesis of periodic breathing in heart failure and the malignant phase of essential hypertension, how often, remains to be determined. Presumably, the increased intracranial tension accentuates the circulatory disturbance in the medulla due to the heart failure.

Decrease in Cerebral Blood Flow.—It has repeatedly been suggested that decrease in circulation through the medulla may be concerned in the production of Cheyne-Stokes breathing. Greeley and Greeley[12] have produced periodic breathing experimentally by curtailment of blood flow through the brain of the morphinized dog; the reader is referred to their paper for a discussion of the mechanisms involved, which seem obscure It has appeared to me that Cheyne-Stokes breathing is especially common in those cases of hypertensive and arteriosclerotic heart failure in which there are palsies or other signs of arteriosclerotic disease of the brain. However, it does not seem that anatomically demonstrable changes in the medulla or its vessels are often concerned, for in histological examinations of the medulla in 12 cases with Cheyne-Stokes breathing, Rosenblueth and Wassermann[24] found arteriosclerotic changes in only one. Cheyne-Stokes breathing is especially apt to ensue in hypertensive and arteriosclerotic heart failure after the blood pressure has fallen somewhat, and this factor may play a part in cutting down the blood flow through the brain.

Summary.—From the foregoing discussion, it is obvious that the pathogenesis of Cheyne-Stokes breathing in circulatory failure has not been entirely elucidated. It would seem that periodic breathing results from an imbalance among the various coefficients regulating respiration. There is evidence that such imbalance can result from the following derangements.

1. Oxygen deficiency.
2. Decrease in the carbon dioxide content of the arterial blood.
3. Diminution in the sensitivity of the respiratory center.
4. Increase in intracranial tension, which produces respiratory periodicity indirectly through the intermediacy of cerebral circulatory periodicity.
5. Decrease in cerebral blood flow.

Experimentally, it has been shown that each of these coefficients, under appropriate conditions, can produce Cheyne-Stokes breathing. And there is clinical evidence that each of them may participate in the Cheyne-Stokes respiration of human cardiac failure. Most often, if not invariably, it would appear that heart failure results in periodic respiration only through the coincident action of more than one of the above factors. Not uncommonly, indeed, there is clinical evidence that all five factors function in an individual case. The more intimate mechanism through which these factors produce Cheyne-Stokes breathing is largely obscure, in many cases, at least, it may be the transference of the "lead" in the regulation of respiration from carbon dioxide to oxygen, which has been shown experimentally by Douglas and Haldane to produce periodic breathing.

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CHAPTER X

ORTHOPNEA

In each of the varieties of cardiac dyspnea—exertional, paroxysmal, and periodic—the sufferer often finds his respiratory distress much ameliorated when he sits up Such orthopnea may be of varying degrees When slight, an additional pillow may be all the patient requires to render him comfortable. But with maximal orthopnea not only is the victim forced to sit up clasping the side of the bed or chair to fix his shoulder girdle and thereby aid the accessory muscles of respiration, but he insists on having his feet hang down, merely sitting up in bed with the lower extremities horizontal, even though he is comfortably supported, does not suffice him Such orthopneic patients may live for weeks or months in a chair. Even though their lower extremities swell enormously and the grotesquely thickened abdominal wall hangs like an apron, they cannot be persuaded to return to bed In extreme orthopnea, particularly in acute episodes, the victim often does not hold his head and trunk upright even though he be supported in this position so that it costs him no physical exertion, but prefers to bend forward with back and neck flexed, and supported by the upper extremities which clasp the side of the bed or some other support. Less often the patient, particularly when sleeping, prefers to extend his head on top of an elevated pillow

While cardiac dyspnea is the favorite domain of orthopnea, it also occurs in other varieties of shortness of breath. Whenever the vital capacity is greatly diminished, orthopnea is apt to appear, for example, in large pleural effusions or pneumothorax The dyspnea of pneumonia, emphysema, or other pulmonary diseases may or may not be accompanied by orthopnea, probably largely depending on the extent to which the respiratory difficulty is due to diminution in vital capacity In bronchial asthma, orthopnea is often agonizing With tumors or aneurysms compressing the mediastinum, breathing may be easier in the upright or some other position, depending on which posture relieves the compression.

On the other hand, orthopnea is not to be regarded as merely a manifestation of severe hyperpnea. For in hyperpnea, which is not associated with decrease in vital capacity—for example, in diabetic, uremic or other acidosis, severe anemia, fever, or peripheral circulatory failure—no matter how great the hyperventilation, the patient is generally content to remain flat in bed even though his sensorium be unimpaired

PATHOGENESIS OF ORTHOPNEA

There have been a number of attempts to explain the amelioration of dyspnea in the erect posture In general, the mechanism of orthopnea in heart failure has been sought along four main lines:

1. Facilitation of pulmonary ventilation in the upright posture.
2. Diminution in pulmonary engorgement when erect
3 Decrease in venous return to the heart with the upper part of the body elevated.
4. Relief of venous stasis in the medulla when erect.

Pulmonary Ventilation and Orthopnea.—A number of investigators have thought that the cause of orthopnea lies in more efficient ventilation of the lungs in the erect posture Christie and Beams[5] found, in both healthy and orthopneic subjects, that vital capacity is greater with the trunk erect They observed the vital capacity to be greater when sitting in about 80 per cent of their normal subjects; in almost all the remaining 20 per cent, there was little change with posture, and only rarely was the vital capacity greater in the reclining position On the average, their 290 healthy subjects had 5 5 per cent less vital capacity when supine In cardiac patients, the increase in vital capacity on assuming the erect posture was much greater Calhoun[4] and his associates also observed the vital capacity to be greater in the sitting posture Both groups of investigators found that in cardiac patients the vital capacity averaged about 27 per cent greater in the erect position. According to Calhoun *et al.*, the change in vital capacity with posture parallels the severity of the heart failure

Patients with cardiac dyspnea are in the dilemma of having increased ventilation in the face of decreased vital capacity (page 128). The increase in vital capacity in the erect position would therefore seem a very obvious explanation of orthopnea in cardiac dyspnea. That respiration is actually more efficient in the erect posture is shown by the studies of Haldane, Meakins and Priestley,[13] who found that "the recumbent position is normally associated with slowing and deepening of the respiration and that if the deepening is prevented symptoms of anoxemia are produced." In cardiacs, the diminution in vital capacity may be great enough to prevent such compensation by deepening of respiration when the patient is reclining, and orthopnea results

The significance of the increased vital capacity in the erect position for the pathogenesis of orthopnea has not gone altogether unquestioned Ernstene and Blumgart[9] found that in their orthopneic patients the vital capacity averaged only 8.3 per cent less in the recumbent than in the most comfortable position, which was not necessarily the erect posture They detected no close correlation between the degree of orthopnea and the reduction in vital

capacity. Ernstene and Blumgart also observed that flexing the head on the thorax of the recumbent patient may relieve orthopnea, although this maneuver exerts no constant influence on the vital capacity However, they admit that in the patients who show a notable increase in vital capacity on assuming the erect posture, this factor must play some part in relieving the dyspnea.

The mechanism of the increase in vital capacity in the erect posture is discussed below (page 175).

Bohr,[8] Rubow,[21] and Hofbauer[17] believe that facilitation of blood flow through the lungs in the erect posture is significant in the genesis of orthopnea The former investigators attribute this to an increase in middle capacity—which measures the average distention of the lungs—in the erect posture. But since the pulmonary engorgement generally responsible for orthopnea results from failure of the left heart, lessened resistance to blood flow in the lungs can hardly alleviate it.

Diminution in Pulmonary Engorgement When Erect.—It has been seen in Chapter VII that pulmonary engorgement is much the most important factor in the pathogenesis of cardiac dyspnea. This fact immediately suggests that orthopnea may be due to increase in pulmonary engorgement in the recumbent posture. There is abundant evidence that this is the case.

Clinical observation immediately reveals a striking parallelism between orthopnea and pulmonary engorgement. The domain *par excellence* of cardiac orthopnea is failure of the left side of the heart with its resultant pulmonary engorgement In isolated left heart failure, in which there is pulmonary engorgement but neither systemic venous engorgement nor fall in arterial pressure, there may be the most violent orthopnea, for example, during attacks of cardiac asthma. Such observations point immediately to pulmonary engorgement as a factor in the production of orthopnea. This inference is immediately supported by the frequent amelioration or relief of orthopnea when right heart failure is superadded to insufficiency of the left heart. It has long been known that in patients with arterial hypertension, coronary sclerosis, or aortic or mitral valvular disease, sudden failure of the right heart—as often accompanies the onset of auricular fibrillation—with increase in venous pressure, swelling of the liver, and edema of the feet, may be quickly followed by relief of dyspnea and especially orthopnea From highly dropsical cardiac patients reclining flat in bed, I have often obtained the history that they had to sit up to breathe prior to the onset of the edema, and have on many occasions observed the transition It is difficult to explain this amelioration of orthopnea with the onset of right heart failure other than by lessening of pulmonary congestion. True enough, there are many patients with edema and other evidences of failure of the right heart who are

also orthopneic. But in these cases examination reveals that, *despite the insufficiency of the right heart, pulmonary engorgement* is pronounced, or that the failure of the right ventricle is secondary to emphysema or other pulmonary disease which of itself decreases the vital capacity and thus predisposes to orthopnea

The question then arises of the mechanism of the relief of pulmonary engorgement in the erect posture Hill[15] long ago expressed *the opinion that orthopnea is due to the retention of blood in the* splanchnic area and lower extremities when the trunk is erect, thus lessening pulmonary congestion. There is good evidence that this is true. Observation of the superficial veins of the lower extremities reveals that the quantity of blood within them is increased in the erect posture. This observation is supported by the plethysmographic *studies of Atzler and Herbst,*[1] *who showed that the volume* of the foot increases in the sitting and erect postures The displacement of blood to the lower part of the body in the vertical posture was demonstrated by Mosso[20] by the following ingenious experiment: A horizontal board was so balanced that when a man first reclined on it the horizontal position was maintained. But as *the man continued in this position, the cephalic end became heavier,* showing that when the subject had been in the erect posture before reclining on the board, blood had accumulated in the caudal part of the body, which was displaced upward as he reclined on the board. By using balanced weights, Mosso found that the upward displacement of blood in this experiment amounted to from 100 to 260 cc. *Since the displacement of blood to the lower extremities* in the erect posture is a result of gravitational influence, it seems a fair assumption that the same is also true in the splanchnic area.

The position adopted by many individuals with orthopnea is one well suited to diminishing pulmonary congestion by displacing blood to the lower extremities For in severe cases the patient is not content merely to sit up, but insists on hanging his feet down from the side of the bed Patients of this type will sit for weeks and months in an easy chair, despite the increasing swelling of the lower extremities, a symptom which is generally a source of great fright to cardiac patients, they cannot be persuaded to sit up in bed with the lower extremities horizontal It has repeatedly been observed that elastic bandaging of the lower extremities with resultant stagnation of blood within them helps to relieve orthopnea.

Not only is blood displaced caudally with the assumption of the erect posture, but the studies of Wollheim[27] indicate that a considerable portion of the displaced blood is withdrawn from the rapid circulation. He found that in cardiac patients whose dyspnea was relieved when they sat up, the *circulating* blood volume decreased from 400 to 1200 cc. in the erect posture.

Diminution in pulmonary engorgement as a result of caudal

displacement of blood is probably the main cause of the orthostatic increase in vital capacity and consequent relief of dyspnea in patients with failure of the left heart. However, another element may also enter Engorgement renders the lung more rigid (page 122), with the consequence that more work has to be performed by the muscles of respiration, and expiration is probably no longer effected purely by the elastic recoil of the lung as in health. The accessory muscles of respiration are called into play—as is often obvious on inspection of an orthopneic patient—to overcome the rigidity of the lung, and this is best accomplished in the erect posture. The lower position of the diaphragm in the erect posture presumably also helps to increase the vital capacity.

Decrease in Venous Return to the Heart.—If the volume of blood returning to the heart per minute in the great veins were diminished in the erect posture, pulmonary engorgement would be lessened and dyspnea relieved Such diminution in venous return entails equal decrease in cardiac output. An attempt to afford a quantitative basis for such an explanation of orthopnea along the lines of diminished cardiac output was made by Field and Bock.[10] Using a carbon dioxide method of measuring the volume of circulation, they found in 13 healthy subjects that the average blood flow when sitting was only 76 per cent, and when standing only 50 per cent, of that when the subject was reclining The decrease in stroke volume in standing was even more marked, for it was only 35 per cent of that in the horizontal position. Henderson and Haggard[14] obtained similar results with the ethyl iodide method. In accord with these findings, Thompson, Alper and Thompson[26] found that a dye injected into a foot vein takes a much longer time to reach an arm vein when the subject is standing than when he is recumbent. Likewise, Bock, Dill and Edwards[2] noted that the circulation time as measured by the histamine method indicates retardation in the velocity of blood flow in the erect position. There are also roentgenological observations by Moritz[19] and Dietlen[6] that the heart is larger in the horizontal than in the vertical posture, which would indicate increased venous return in the former position. But in view of the coincident change in the height of the diaphragm and perhaps other factors, it is not certain that such observations furnish an accurate measure of the volume of the heart.

These findings seemed to have shown that the venous return and cardiac output are greater in the recumbent than in the erect posture. But contrary results were obtained by Grollman[12] and Marshall.[18] With the acetylene method (page 36), they detected no difference which they considered significant in the two positions However, using his modification of the acetylene method (page 36), Gladstone[11] found in 34 consecutive determinations in 6 healthy young men that the cardiac output is between 10 and 25 per cent

greater in the recumbent than the erect posture. Similarly, Donal, Gamble and Shaw[7] with the improved ethyl iodide method and Schneider and Crampton[23] with the acetylene method found that the cardiac output is less in the erect posture, and Scott[24] observed that this is usually the case Using Gladstone's modification (page 36) of the acetylene method, Sweeney and Mayerson[25] found the cardiac output from 8 to 36 per cent higher in the recumbent posture.

The weight of evidence thus strongly indicates a greater venous return to the heart in the recumbent than in the erect posture Such increased venous return when recumbent would obviously augment pulmonary engorgement in the reclining patient and thus favor dyspnea.

Venous Stasis and Orthopnea.—Since the venous return from the head in the erect posture is aided by gravity, it has been thought that the relief of venous stasis in the medullary respiratory center plays a part in the relief experienced by orthopneic patients on sitting up. This view was enunciated briefly by Sahli[22] and Hirschfelder.[16] However, it has been brought to the fore only recently as the result of a detailed study by Ernstene and Blumgart.[9] They found that in cardiac patients there is a definite parallelism between the degree of orthopnea and the venous pressure They also observed that merely flexing the head of an orthopneic patient may notably relieve his distress, although such a maneuver has little effect on the vital capacity Eppinger, Laszlo and Schuermeyer[8] also believe that orthopnea results from impaired circulation through the respiratory center in the horizontal position They base this view on experiments with the thermostromuhr, in which they found that lowering the head decreases the rate of blood flow in the internal jugular vein. Eppinger and his associates also call attention, in this connection, to the fact that the cerebral pulsations are smaller in the horizontal position. They were able to diminish the cerebral pulsations by slight pressure on the neck, presumably owing to interference with the venous return from the head. Their deduction is that increased venous pressure in cardiac failure similarly interferes with the circulation through the respiratory center, and this effect is accentuated in the horizontal position.

The theory of decreased cerebral blood flow in the recumbent position as the essential cause of orthopnea has been controverted by Calhoun and his associates[4] In comparative studies of the blood from an artery and from the internal jugular vein, they found no difference in the amount of oxygen abstracted from the blood passing through the brain of orthopneic patients in the erect and recumbent positions. This shows that there was no considerable difference in the blood flow through the brain in the two positions. Nor did they produce dyspnea by increasing the intracranial venous

pressure by moderate constriction of the neck with a blood pressure cuff.

Nor do clinical observations indicate that engorgement of the systemic veins is significant in the production of orthopnea. As mentioned above, orthopnea is common in isolated left heart failure with normal venous pressure, and is often relieved when the right heart fails with the development of high systemic venous pressure. And it is very striking in the rare cases of primary right heart failure due to such causes as pulmonary or tricuspid valvular defects or pulmonary endarteritis (page 544), that orthopnea may be absent despite extreme cyanosis and enormously engorged veins

Orthopnea in Hypodiastolic Failure.—Under this caption are included those instances of cardiac failure which are due to interference with diastole, either as a result of mechanical incarceration of the heart by pericardial effusion or shrinking adhesive mediastinopericarditis or of shortening of diastole in extreme tachycardia The degree of orthopnea varies greatly. In many instances of copious pericardial effusion, there is agonizing orthopnea, which is immediately relieved by paracentesis. Such cases usually present other evidences of pulmonary stasis, presumably due to compression of the pulmonary veins or left auricle, and it seems probable that the orthopnea is correlated with pulmonary engorgement. Contrariwise, there are cases of mediastino-pericarditis in which, despite high venous pressure, a large liver, and recurrent ascites, there is no orthopnea and but moderate dyspnea, the roentgen picture of the lungs then reveals little engorgement.

The Absence of Orthopnea in Peripheral Circulatory Failure.—In peripheral circulatory failure with shock, orthopnea is absent, although there is often pronounced hyperpnea. In fact, the patients seem more comfortable with their heads low. These observations show that decrease in cardiac output, which is surely very low in shock, does not cause orthopnea and in fact tends to counteract it

Summary.—It seems evident that the orthopnea of heart failure is almost exclusively a manifestation of pulmonary enlargement The amelioration of dyspnea in the erect posture is due to an increase in vital capacity. This increase in vital capacity is predominantly a result of redistribution of blood, whereby with the assumption of the erect posture blood is shifted from the lungs to the splanchnic area and lower extremities and some is withdrawn from the active circulation The preponderance of evidence indicates that the main factor in producing this redistribution of blood is that as a result of gravitational influence the venous return to the heart from the dependent portions of the body is diminished in the erect posture. The vital capacity is probably also increased in the erect posture as a result of more effective use of the accessory muscles of

respiration, which are called into play to overcome the rigidity of the engorged lung.

The dependence of cardiac orthopnea on pulmonary engorgement explains why this symptom is predominantly a manifestation of failure of the left side of the heart. Failure of the right ventricle tends to alleviate orthopnea, presumably through diminishing pulmonary engorgement

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CHAPTER XI

CYANOSIS

BLUISH discoloration of the skin and mucous membranes is a common manifestation of circulatory failure, be it of cardiac or peripheral origin In congenital heart disease, however, cyanosis may arise from the admixture of venous and arterial blood in the absence of circulatory failure

In its lesser degrees, cyanosis is discernible only in certain areas, especially the lips and the tips of the fingers and toes, particularly in the nail beds In these parts, the integument is thin and the small vessels* superficial and fairly thick set, so that even in health the color of the blood shows through to a greater extent than elsewhere (the terminal phalanges are almost always redder than the others). That such enhanced "visibility" of the blood is a fundamental reason why cyanosis is generally seen first in these areas is shown by the fact that they are also the sites of election for the detection of slight cyanosis when the latter is of purely pulmonary origin, as in pneumonia without circulatory failure. An additional factor is that the tips of the fingers and toes are end-points of the circulation so that when slowing of blood flow with consequent increase in the reduction of oxyhemoglobin participates in producing cyanosis, as in heart failure, the blueness is also most pronounced in these areas In some individuals, cyanosis appears early at the tip of the nose, over the cheek bones, and in the ears This is often seen strikingly in persons with originally ruddy complexions or numerous dilated small vessels on the face as a result of long life in the open and exposure to wind. The mucous membranes of the mouth and conjunctiva and the retina often show the discoloration in its incipiency, especially when it is arterial in origin. When the cyanosis becomes more intense, almost the entire body surface may be involved. However, the scleræ and other regions of minimal vascularization are generally spared

In peripheral circulatory failure with shock, the cyanosis may have a remarkable distribution in the dependent parts of the body. Thus, in a woman with peripheral circulatory failure following an extensive burn, the dorsal aspect of the body was cyanotic, ter-

* Lewis[13] shows that throughout most of the body the contribution of the blood to the skin color is due mainly to that contained in the subpapillary venous plexus, while the capillaries are of less significance He states that in the hand and in the sole of the foot, where the capillaries are most numerous, their share in the skin coloration is more significant Wollheim[17] also emphasizes the great significance of the subpapillary venous plexus for cyanotic discoloration of the skin Of course, dilatation of the capillaries increases their contribution to the color of the skin

minating ventrally in a horizontal line (in the recumbent patient) like the water line of a ship; the appearance resembled that of cadaveric lividity, and indeed there could be no doubt that in the still mentally alert woman there was a gravitational hypostasis of the blood. In other forms of shock (*e. g.*, in acute pancreatitis) the cyanosis may have an irregularly patchy distribution, to which may be added the usual acrocyanosis.

The hue of the cyanosis varies and may be of diagnostic significance. The usual blue deepens to almost inky black in maximum cyanosis. In the cyanosis of shock, in which the capillaries are poorly filled, the blue tends to become grayish or leaden. When an individual with high hemoglobin content and increased circulating blood volume becomes cyanotic, the color is a bluish-red. When heart failure has produced icterus, a peculiar coloration results from the admixture of blue and yellow—so-called cyanotic icterus. In influenzal and other severe varieties of bronchopneumonia, the cyanosis is on rare occasions of a peculiar hue which has been compared to that of heliotrope or lilac (Abrahams, Hallows and French[3]) Cyanosis is, of course, difficult to distinguish in the negro. Since cyanosis is due to the color of the blood, it is removed by pressure. In an edematous area, cyanosis tends to be dissipated Cyanosis often lessens so rapidly after death that the pathologist does not observe it in the skin, but in other instances it is very striking on the postmortem table

Cyanosis is to be differentiated from *erythrosis*, the brick-red color of the skin in polycythemia vera without pulmonary complications or circulatory failure, which results from increased hemoglobin content of the blood and better filling of the superficial capillaries as a result of the augmented circulating blood volume. In practice, however, the differentiation on inspection is sometimes uncertain; for reasons to be mentioned below, patients with erythrosis readily become cyanotic

OCCURRENCE OF CYANOSIS IN HEART DISEASE

Cyanosis may occur in any of the types of heart failure or in circulatory insufficiency of peripheral origin. The details of the occurrence of cyanosis will be considered with the individual causes of circulatory failure. Here it may be remarked that, in general, cyanosis tends to predominate over dyspnea in right heart failure and dyspnea over cyanosis in insufficiency of the left side of the heart Most intense cyanosis is seen when the right heart failure is secondary to pulmonary disease, as in emphysema or especially the rare instances of primary disease of the pulmonary artery ("black cardiacs") Pulmonary edema, large pleural effusions, and pneumonia *or extensive pulmonary infarcts are frequent causes of*

deepening of cyanosis in cardiac patients. Pulmonary embolism may lead to cyanosis of acute development and maximum intensity. Another cause of acrocyanosis of remarkable depth is occlusive thrombosis of the left auricle (page 521). Congenital heart disease with or without cardiac failure is, of course, the classical domain of cyanosis, which may be paroxysmal (page 187).

In general, cyanosis in cardiac disease tends to be deeper the higher the hemoglobin content of the blood It will be seen in the next section that if anemia is sufficiently severe, cyanosis cannot develop.

It should be remembered that cyanosis is a much less common manifestation of heart failure than is dyspnea. Especially left heart failure may be of maximum severity in the absence of cyanosis. Indeed, many patients with failure of the left side of the heart are strikingly pale as a result of peripheral vasoconstriction.

PATHOGENESIS OF CYANOSIS

An important element in the color of the skin is that contributed by the blood in the superficial venules and capillaries. Disregarding the normally insignificant yellow pigmentation of the plasma, the color of the blood is the additive resultant of the bright red contributed by the oxyhemoglobin and the blue of the reduced hemoglobin *We speak of cyanosis when the contribution of the reduced hemoglobin to the skin color becomes marked enough to influence it discernibly in the direction of blue.*

The primary condition, then, for the production of cyanosis is an increase in the concentration of reduced hemoglobin in the blood of the venules and capillaries. The quantitative elucidation of the conditions for the development of cyanosis is due largely to the classic investigations of Lundsgaard and Van Slyke;[13] they may be summarized briefly as follows:

In health, the blood has an oxygen capacity of about 20 volumes per cent, *i. e.*, the hemoglobin of each 100 cc. of blood can combine with 20 cc. of oxygen The arterial blood is, however, generally only about 95 per cent saturated, so that the actual oxygen content is about 19 volumes per cent. The extent of the reduction of the hemoglobin varies in different vascular territories, but averages about 5 volumes per cent, so that the venous blood contains about 14 volumes per cent of oxygen. In other words, the unsaturation (following Lundsgaard and Van Slyke, in connection with cyanosis it is more convenient to speak of unsaturation) of the arterial blood is 1 volume per cent and of the venous blood 6 volumes per cent of oxygen And the mean capillary unsaturation in health is

$$\frac{1 + 6}{2} = 3.5 \text{ volumes per cent of oxygen}$$

The value that is of primary interest in connection with cyanosis is the *average* capillary unsaturation. For it is obvious that loss of oxygen at the beginning of the capillary will have much greater effect in producing cyanosis than an equal loss at the venous end of the capillary. Unfortunately, the figure derived above by taking the arithmetical *mean* of the arterial and venous unsaturations does not represent exactly the *average* unsaturation of the capillary blood since it is hardly likely that the loss of oxygen proceeds uniformly during the transit of a capillary. The principal factors preventing such uniformity are given by Lundsgaard and Van Slyke as follows:

1. At the arterial end of the capillary, the tension of oxygen is the highest, so that it tends to be given off most rapidly here.

2. The dissociation curve of oxyhemoglobin is not rectilinear but is such that at lower oxygen tensions more of the gas is given off for an equal drop in pressure. This factor promotes oxygen loss at the venous end.

3. The entrance of carbon dioxide from the tissues into the blood increases the dissociation of oxyhemoglobin The influence would also tend to increase the oxygen loss at the venous end

Slowing of the rate of blood flow in the course of the capillary and variations in the caliber of the latter would also militate against uniform loss of oxygen In patients with right heart failure, the venous limb of the capillary is dilated, so that blood flow is much slower here.

Available data do not permit differentiation of the significance of these factors. However, they neutralize one another to at least a considerable extent, so that Lundsgaard and Van Slyke have used the arithmetic mean of the arterial and venous capillary unsaturations for the average capillary unsaturation, and the studies of Henderson[11] show that actually this is approximately so

Lundsgaard found in a considerable series of cases that cyanosis appears when the mean capillary unsaturation is of the order of 6 to 7 volumes per cent. Since 1 cc. of oxygen combines with about 0 75 gram of hemoglobin, this threshold value for cyanosis corresponds to about 5 grams of reduced hemoglobin per 100 cc of blood.

There are two important corollaries of Lundsgaard's principle that the presence or absence of cyanosis depends on the absolute concentration of reduced hemoglobin in the blood. In the first place, cyanosis occurs more readily the greater the hemoglobin content of the blood, for then the same percentage of unsaturation corresponds to a higher concentration of reduced hemoglobin. This explains why patients with polycythemia become cyanosed so readily On the other hand, and for the same reason, anemia militates against cyanosis. In fact, Lundsgaard points out that individuals with less than 5 grams of hemoglobin per 100 cc. of blood (about 30 per cent on the usual scales) cannot generally become cyanotic

For he found (see above) that 5 grams of reduced hemogl the threshold value for cyanosis, so that even complete unsat with less than this concentration of hemoglobin could not p discernible blueness

In the foregoing, we have considered only the rôle of c in the chemical composition of the blood in the genesis of cy However, in right heart failure with systemic venous engorg another "mechanical" factor enters, namely, distention of th ules and the venous end of the capillaries. A glance at the on the back of the hand shows that normal venous blood p a cyanotic color through the skin. It is therefore eviden sufficient dilatation of the minute venous vessels will produc ness of the skin

Three fundamental mechanisms thus participate in the prod of the cyanosis of circulatory failure; while they may occu pendently, more often they are combined:

1 Deficient oxygenation in the lungs.
2 Increased reduction in the capillaries
3 Distention of the venules and venous ends of the capi

The Pulmonary Factor in Cyanosis.—Obviously, deficien genation of the blood in the lungs can produce cyanosis. I this factor more readily results in cyanosis than does slow capillary flow because inadequately oxygenated arterial affects the color of the blood throughout the length of the capi while the cyanosis of retarded peripheral flow develops only blood proceeds along the capillary. This difference is exp quantitatively in Lundsgaard's formula for the mean ca unsaturation (page 182), as seen in the following illustration:

Suppose that pulmonary changes result in the arterial leaving the lungs with an unsaturation of 4 volumes per c oxygen instead of the normal 1 volume per cent. If, the blood flow through the capillaries is not slowed, so that the loss in them is the usual 5 volumes per cent, the venous unsatu will be $4 + 5 = 9$ volumes per cent. And the mean capillary uration will be $\frac{4 + 9}{2} = 6.5$ volumes per cent of oxygen, would produce cyanosis with the normal hemoglobin cont the blood

On the other hand, consider an instance in which pulm aëration is unaffected but the blood flow through the capilla slowed to such an extent that the loss of oxygen in the capill 8 instead of the normal 5 volumes per cent of oxygen. Here, the venous unsaturation is 9 volumes per cent, but the mean lary unsaturation is only $\frac{1 + 9}{2} = 5$ volumes per cent of o a value that would not lead to cyanosis with normal hemo

concentration. In other words, in our illustration, an increase of 3 volumes per cent in arterial oxygen unsaturation leads to cyanosis, while an equal augmentation of oxygen loss in the capillaries does not.

Actually, in at least the great majority of instances of marked cyanosis in heart failure, diminished oxygen saturation of the arterial blood (Harrop,[10] Barach and Woodwell[4]) evinces the great significance of the pulmonary factor in the production of the cyanosis. Cossio and Berconsky[7] found arterial oxygen unsaturation concerned in the pathogenesis of the cyanosis in only 10 of 20 cyanotic patients with mitral stenosis, but this proportion appears lower than that generally observed. The importance of the pulmonary factor is also shown in many cases by the clearing up of the cyanosis if high concentrations of oxygen are breathed. The most extreme degrees of cyanosis are generally observed in those cases in which pulmonary lesions, such as emphysema or the rare pulmonary endarteritis, play a part in the production of the heart failure, or such processes as pneumonia, large infarction, copious pleural effusion, or pulmonary edema complicate cardiac insufficiency. The mechanisms causing inadequate pulmonary oxygenation in heart failure have already been discussed (page 122).

Rôle of Capillary Reduction in Cyanosis.—It has been seen in the preceding section that cyanosis is more readily produced by deficient oxygenation in the lungs than by increased reduction in the capillaries. Nevertheless, the latter is also an important factor in many instances of cyanosis in circulatory failure. In fact, there are patients in whom cyanosis is entirely due to increased reduction in the capillaries, the oxygen saturation of the arterial blood being within normal limits. Such cases, due to heart failure in hypertension have been published by Schoen and Derra,[15] in one of their patients the arteriovenous oxygen difference was 11 2 volumes per cent. More commonly, however, cyanosis due entirely to increased reduction in the capillaries is a manifestation of peripheral circulatory failure with shock. Schoen and Derra studied 2 such cases in which the cyanosis was entirely of capillary origin with normal oxygen saturation of the arterial blood Cossio and Berconsky observed 6 patients with mitral stenosis in whom the cyanosis was due entirely to greater peripheral utilization A measure of the significance of the peripheral capillary factor in the production of cyanosis is afforded by the arteriovenous oxygen difference, which expresses the reduction in the capillaries.

Several mechanisms may participate in augmenting capillary reduction in circulatory failure:

1. As a result of heart failure, the *vis a tergo* may be so greatly diminished as to retard notably the blood flow through the capillaries and thereby result in preternaturally great loss of oxygen

2. In those forms of shock in which the circulating blood volume and cardiac output are greatly diminished, there may be some compensation for the reduced blood flow by more thorough capillary reduction.

3. In shock in which there is capillary "paralysis," the capillary bed may be so dilated that blood flow is significantly slowed and an abnormally great surface presented for exchange between blood and tissues. The pathogenesis of such cyanosis is perhaps analogous to what occurs in acrocyanosis of vasomotor origin, in which Boas[6] observed and figured clearly the enormous increase in length and width of the capillaries of the nail fold, which also exhibited many convolutions and a bizarre arrangement

4 The increased oxygen consumption in heart failure must be met, to the extent that the weakened heart does not sufficiently increase cardiac output, by more thorough capillary reduction.

Distention of the Venules and Venous Ends of the Capillaries.—Right heart failure with increase in venous pressure results in distention of the venules and the venous ends of the capillaries Mueller[13] found that if a blood pressure cuff around the arm be inflated to about 60 mm of mercury, the number of open and blood-filled capillaries seen in the nail fold increases, as does their length and width Mueller and others have shown that in heart failure with venous stasis the venous limbs of the capillaries of the nail fold are greatly dilated and the flow through them so slowed that the blood column appears discontinuous. In such cases, the number of capillaries visible is so great that Mueller weighs the possibility that not only is the entire normal quota of capillaries simultaneously opened, but that there may also be newly formed capillaries Further, the small subpapillary venules are so distended that they must contribute notably to the cyanosis. Goldschmidt and Light[8] have shown in healthy subjects that mechanical distention of the capillaries and venules by increased venous pressure can produce cyanosis even though the capillary unsaturation of the blood in these vessels is normal. In patients with circulatory failure, Wollheim[17] found with the capillary microscope that the distention and filling of the subpapillary venous and capillary networks of the skin parallels the cyanosis. Harrison[9] has demonstrated that in some patients with slight cyanosis due to heart failure both the arterial and the venous oxygen unsaturations are normal, indicating that the cyanosis is due to the distention of the minute venous vessels

The increased circulating blood volume present in many patients with cardiac cyanosis probably also contributes to the filling of the venules and venous capillaries and thereby to the cyanosis Indeed, Wollheim believes that one factor in producing cyanosis in heart failure is a "compensatory" storage of blood in the subpapillary

venous and capillary networks of the skin, which tends to counteract the increase in circulating blood volume and thereby unburdens the heart.

The filling of the venules and capillaries influences the hue of the cyanosis. Thus, in heart failure with large circulating blood volume, in which the minute vessels of the skin are well filled, the cyanosis is apt to be a dark blue or purple. On the other hand, in peripheral circulatory failure, with its poorly filled vessels, the skin tends toward a grayish color

CYANOSIS IN CONGENITAL HEART DISEASE

Congenital heart disease is the classical domain of cyanosis Nevertheless, cyanosis is absent in many varieties of congenital cardiovascular defects, and in others appears only after many years or paroxysmally. From the point of view of the occurrence and pathogenesis of cyanosis, two general groups of cases may be recognized:

1. Cases in which cyanosis is absent or, if it appears, is purely a manifestation of heart failure. This group comprises cases in which there is no abnormal communication between the right and left sides of the circulation Included are such conditions as coarctation of the aorta, congenital arteriovenous fistula, and congenital aortic, mitral, and pulmonic stenosis. It may be worthy of emphasis that uncomplicated pulmonic stenosis, a very rare condition, may be present for years without cyanosis, or the patient may succumb to pulmonary tuberculosis without other than terminal cyanosis *The pathogenesis of cyanosis in these cases is essentially* the same as in heart failure due to acquired lesions, and has been discussed in the preceding sections

2. Cases in which an abnormal communication between the right and left sides of the circulation is concerned in the pathogenesis of the cyanosis Included are such conditions as patent ductus Botalli and foramen ovale, interventricular and interauricular septal defects, transposition of the great vessels, and the tetralogy of Fallot (pulmonic stenosis, interventricular septal defect, dextroposition of the aorta, and hypertrophy of the right ventricle), the latter of which is the most common form of cyanosis of congenital origin to pass adolescence. In these cases, the cyanosis is due to the entrance of sufficient venous blood from the right half of the circulation through the abnormal communication into the left half of the circulation to influence the blood of the latter perceptibly in the direction of blue. Lundsgaard and Van Slyke showed that, the hemoglobin content and other conditions being normal, the venous arterial shunt must amount to about 38 per cent of the total cardiac output to produce discernible cyanosis. But under the conditions

of congenital heart disease, a smaller shunt doubtless often suffices to produce cyanosis. For many of the patients have polycythemia of high degree and increase in circulating blood volume, factors which have been seen above to lower the percentage of oxygen unsaturation of the arterial blood necessary to produce cyanosis. Pulmonary or peripheral stasis may also participate in the causation of the cyanosis. Finally, the degree of oxygen unsaturation of the contaminating venous blood is of significance for its effect in producing cyanosis.

Since the cyanosis depends primarily on the quantity of venous blood that enters the left half of the circulation through the anomalous opening, it is not surprising that cyanosis is not always present even in cases with communications between the two sides of the circulation. Thus, in most instances of patent ductus, persistent foramen ovale, or interventricular or interauricular septal defects, cyanosis is absent for years or permanently. Analyses of the arterial blood in such cases have revealed normal oxygen saturation, indicating that the quantity of venous blood entering the left side of the circulation is negligible. Evidently, the higher pressure in the left side of the circulation results in an arterial venous and not venous arterial shunt However, some such patients become cyanotic on exertion; perhaps the increased venous return so raises the pressure in the right side of the circulation that the direction of the shunt is reversed to venous arterial, and the more thorough reduction of the blood in the exercising muscles increases its effect in producing cyanosis Ultimately, though sometimes only after many years and preterminally, many of these cases become cyanotic—the *cyanose tardive* (delayed cyanosis) long ago described by Bard and Curtillet[5] in an individual with patent foramen ovale. This phenomenon is also believed to be due to a reversal of the shunt from arteriovenous to venous arterial as a result of heart failure, pneumonia, or other and as yet obscure causes which raise the pressure in the right side of the heart. But it is to be emphasized that many of the patients succumb to accidental complications or bacterial endocarditis without ever becoming cyanotic.

In other instances of abnormal communication between the two halves of the circulation, there is persistent cyanosis from an early period of life. The most frequent cause in those passing childhood is the tetralogy of Fallot, in which the high pressure in the right ventricle resulting from the pulmonic stenosis produces a venous arterial shunt through the interventricular septal defect and in which there is also dextroposition of the aorta so that blood is poured into it from both ventricles Various other congenital defects may also produce persistent cyanosis (Abbott[1]).

A number of attempts have been made to calculate, from the oxygen unsaturations of the arterial and venous bloods and certain

other data, the size of the venous arterial shunt in cases of persistent cyanosis (for the formulas, which involve the assumption of data that cannot be determined experimentally, see Lundsgaard and Van Slyke and Segall[16]). In a detailed study by Segall of a patient with the tetralogy of Fallot, he calculated the venous arterial shunt as being of the order of 75 per cent of the total cardiac output.

For further information concerning cyanosis in congenital heart disease, the reader is referred to the classical articles of Abbott[1] and Abbott and Weiss[2]

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CHAPTER XII

EDEMA

Dropsy is a common manifestation of cardiac insufficiency. Transudates due to heart failure may accumulate either in the territory drained by the venæ cavæ, as a result of weakness of the right heart, or in the lungs, most often in consequence of insufficiency of the left heart. Although the term cardiac edema is, of course, applicable to both distributions, the present chapter will be restricted to systemic dropsy, postponing consideration of pulmonary edema to Chapter XIV.

There may be considerable retention of water in the organism as a result of heart failure before it is demonstrable in the form of pitting edema or a serous effusion—so-called pre-edema. This occult water retention is especially apt to develop in bed-ridden patients, for in the ambulant, swelling around the ankles generally appears before the fluid retention becomes great. Such occult fluid retention is best followed by weighing the patient; it may amount to 10 or even 20 pounds. Often an individual with heart failure loses 10 or more pounds following digitalization although no edema had previously been demonstrable.

CLINICAL FEATURES OF CARDIAC EDEMA

An outstanding characteristic of cardiac edema is the influence of gravity in determining its distribution. For this reason, cardiac edema in ambulant patients is most often first detectable in the lower extremities in the vicinity of the internal malleolus and the inner surface of the tibia, where the underlying bone renders pitting easy to elicit. Such incipient swelling generally evolves during the day as the patient is up and about, to be noticed when undressing in the evening, and clearing up after a night's rest in bed. It may be seen only distal to some constriction, as the strap of a woman's shoe, or beneath an encircling garter. Usually, this initial swelling is symmetrically bilateral, but local influences, such as varicose veins, may cause the edema to appear first in one limb. In bed-ridden patients, cardiac edema often appears first over the sacrum or, especially in the obese, at the dorso-medial aspect of the thigh, where it may be detected early by pinching a fold of the thickened skin between the fingers. If the patient sleeps on one side, the edema may be confined entirely to that half of the body; or if one hand hangs down, to that extremity. In obese, orthopneic patients who sit up in a chair for weeks, the abdominal wall may be enormously infiltrated and hang down like a grotesque apron.

It is thus seen that the initial localization of cardiac edema is characteristically different from that of the edema of acute glomerulonephritis, which generally appears first in the face and particularly the eyelids, and is usually most evident in the morning on arising Similarly, nephrotic edema in the nephrotic stage of glomerulonephritis or chronic nephrosis may first appear in the face, although very often the swelling in these cases manifests itself initially in the lower extremities as does cardiac edema Early swelling of the face in cardiac edema has been described (Resnik and Keefer[37]), but I have not seen this apart from large pericardial effusions or compression of the superior vena cava

With extension of the edema, almost the entire body surface may be involved, although the face is almost always spared. At the necropsy of a patient who died with massive cardiac dropsy, edema of the mucous membranes and the connective-tissue framework of various viscera may be found To what extent gastro-intestinal or other symptoms result from such internal edema remains to be determined. The redoubtable edema of the glottis occasionally occurs in hypertensive or arteriosclerotic patients in the absence of other edema, but it does not seem to result from cardiac failure alone. Edema of the prepuce may cause difficulty in urination; and dropsical swelling of the scrotum may produce considerable discomfort. In patients with cardiac edema the pressure of the cerebrospinal fluid is generally elevated, but there does not seem to be any increase in the volume of the fluid (page 277). At necropsy, the meninges, especially the leptomeninges, may be gelatinous and swollen as a result of edema The brain substance may also be edematous (page 276).

Cardiac edema, unless very massive, is usually not as soft as is nephrotic edema; the pitting produced by pressure disappears more rapidly than in the latter, presumably as a result of the greater turgidity of the skin due to the engorgement of the capillaries and venules As a result of the congestion, further, the edematous limb in cardiac failure most often does not have the dead white appearance of nephrotic edema. But in exceptional instances with very voluminous edema, the swelling may be white and soft, masking cyanosis seen in non-edematous parts and not to be distinguished from nephrotic or nephritic edema That jaundice is masked by edema is mentioned on page 258. After the edema has been present for a long time, thickening and hardening of the skin develops as a result of swelling and proliferation of the collagenous elements; with this, the skin does not pit as readily, is often somewhat reddened or pigmented, and feels brawny and rough. On occasions, rare nowadays, tremendous edema results in rupture of the skin with drainage of dropsical fluid, which may persist for a long time Edematous skin, particularly if incised or punctured, is susceptible

to erysipelas and other infections, but in my experience this is far more rare with cardiac than with nephrotic anasarca.

As regards the *composition of the edema fluid* obtained by subcutaneous drainage in cardiac dropsy, it has long been known to contain less solid matter than the transudates into the serous cavities The specific gravity is low, between 1.005 and 1.010. The protein content is intermediate between the highly albuminous fluid of acute glomerulonephritis and inflammatory edemas and the almost protein-free fluid of nephrotic edema. The investigations of Epstein,[15] Bramkamp,[6] and others show that it contains between 0 03 and 0 5 per cent—with an average of 0.21 per cent in 24 cases studied by Bramkamp—of protein, which is much less than the protein content of the concomitant transudates in the serous cavities (page 200) So far as is known, the crystalloids in the fluid of cardiac dropsy are present in concentrations similar to those in nephrotic edema For a detailed discussion of the concentrations of the electrolytes in transudates and what is known of their *rationale* the reader is referred to the recent work of Peters,[34] comparative analyses of the composition of edema fluid, pleural transudate, and the blood in 22 cases of heart failure have been published by Reiche.[35] Here, it will merely be mentioned that chloride is present in higher concentration than in the blood; that the concentrations of the other electrolytes confirm fairly well to what would be expected on the basis of the Donnan equilibrium; and that the urea and sugar content are about equal to that of the blood.

PATHOGENESIS OF CARDIAC EDEMA

According to the conception evolved in masterful fashion by Starling,[40] the fundamental mechanism regulating the exchange of fluid between the capillaries and the tissue spaces is represented by an equilibrium between the opposing colloid osmotic and hydrostatic pressures of the blood in the capillaries.* Displacement of this equilibrium in favor of the colloid osmotic pressure results in resorption of fluid from the tissue spaces into the blood, while relative preponderance of the hydrostatic pressure produces accumulation of fluid in the tissue spaces Of course, the fluid exchange between the blood and the tissue spaces is also affected by a multitude of other moments, notably nervous, hormonal, the chemical and physical properties and concentrations of various electrolytes and other substances, the metabolic activities of the tissue cells,

* By direct microscopic studies, Landis[28] has found the hydrostatic pressure in the capillaries in the skin at the base of the human finger nail to be 32 mm of mercury in the arterial limb and 12 mm in the venous limb The colloid osmotic pressure of human plasma in health is about 25 mm of mercury. The equilibrium between the colloid osmotic pressure and the hydrostatic pressure is thus adapted to transudation in the arterial and resorption in the venous limb.

the function of the kidneys, and perhaps true secretory processes by the endothelium of the blood and lymph capillaries However, the fundamental regulation seems to be through the above-mentioned equilibrium, and it is readily conceivable, though decidedly not proved at the present state of knowledge, that these other factors exert their effects, in the last analysis, through displacement of the equilibrium between the hydrostatic and the colloid osmotic pressure of the blood in the capillaries. At any rate, such a working hypothesis has proved decidedly fruitful in attempts at elucidation of the pathogenesis of edema It was first seriously applied in this field in the classical studies of Epstein[13] who adduced strong evidence that the edema of chronic nephrosis and the nephrotic stage of glomerulonephritis results from the diminished colloid osmotic pressure of the blood. Experimental verification of this conception of nephrotic edema was furnished by Leiter[27] and substantiated by Barker and Kirk,[3] who were able to produce edema by experimental depletion of the plasma proteins, which entails a corresponding depression of the colloid osmotic pressure of the plasma.

The work of a number of investigators indicates that *the edema of heart failure is also due primarily to displacement of the equilibrium between the hydrostatic and the colloid osmotic pressures of the plasma in favor of the former.* But in the case of cardiac edema, the *displacement appears to be due principally to increase in hydrostatic pressure.* To a large extent, this represents merely a more precise formulation of the conception held by clinicians of a century ago, to whom the connection between venous (and consequently capillary) engorgement and cardiac edema was evident But with the widespread abandonment of the filtration theories of lymph and urine formation following the work of Heidenhain,[19] this physical conception was largely given up—though clinicians in general could not avoid thinking in terms of it—to be resuscitated in a modern form as a result of the application of Starling's theory, Epstein's clinical and Leiter's experimental work on nephrotic edema, and the studies of Krogh[23] and Landis[25] on the relations between capillary pressure and fluid exchange.

Clinical Correlations of Cardiac Edema.—The occurrence of edema in circulatory failure may be briefly summarized as follows:

1. In right heart failure with engorgement of the systemic veins, edema is common.

2. In hypodiastolic failure due to limitation of the diastole of the heart (mediastino-pericarditis, pericardial effusion) in which the systemic veins are engorged, edema is also frequent and may attain tremendous extent.

3 In left heart failure, in which the systemic veins are not congested, edema is conspicuous by its absence. Left heart failure may exist for years in patients with hypertension and coronary sclerosis,

having recurrent attacks of cardiac asthma and pulmonary edema, but so long as the right heart holds out and the tributaries of the venæ cavæ are not engorged, there is no peripheral edema. During attacks of cardiac asthma lasting hours, the extremities may be cold and of a grayish cyanosis, testifying eloquently to the slowing of the circulation, but while venous engorgement is absent, edema does not appear

4 In peripheral circulatory failure, edema is absent. I have repeatedly seen patients in shock for days, with cyanotic and cold extremities, yet edema was not only absent but the superficial tissues were obviously dehydrated.

It is thus clear that *cardiac edema is correlated with venous engorgement*, a fact with which clinicians have been acquainted for over a century. Further, the absence of dropsy in peripheral failure and left heart failure shows that circulatory retardation *per se* is not a decisive factor in producing edema.

Not only does the occurrence of edema in general circulatory disturbances, as just described, indicate clearly its correlation with venous stasis, but the frequent development of localized edema in the territory of an obstructed vein shows even more obviously that venous stasis can produce edema. That such localized edema results from venous obstruction was denied by Hodgson,[20] but definitely established on large material by Bouillaud.[6] Edema is so often seen in instances of neoplasm, aneurysm, etc., which compress veins that the connection is beyond doubt. Of course, in connection with the presence or absence of edema in localized venous obstruction, the enormous potentialities for collateral circulation in most venous territories and the vicarious function of the regional lymphatics must be borne in mind

Experimental Production of Edema by Venous Obstruction.— In 1680, Lower[29] observed the development of ascites in a dog following the ligation of the inferior vena cava in the thorax. He also ligated the two jugular veins, which was followed by dropsical infiltration of the tissues above the ligature as well as abundant flow of tears and saliva As a result of these experiments, venous obstruction was accepted as a cause of edema, which previously, following the discovery of the lymphatics by Aselli early in the seventeenth century, had been attributed to rupture of the latter.

Two centuries later, however, Ranvier[35] carried out experiments that were thought to contradict this interpretation. He ligated the inferior vena cava of the dog low down, following which edema of the hind limbs did not develop. But when, in addition, he divided one sciatic nerve and thereby produced vasodilatation on that side, edema of the limb appeared within an hour. Similarly, it was found that if the veins to both ears of a rabbit are ligated and the cervical sympathetic cut on one side, edema develops only

in that ear. These experiments were widely considered to disprove the conception that venous obstruction produces transudation by elevating the pressure in the capillaries, and to indicate that vasomotor factors, which could not be more closely defined, were responsible for the transudation However, Cohnheim[5] soon showed that even in Ranvier's experiment it was actually the obstruction to venous return that was responsible for the edema He found that after ligation of the femoral vein in the dog the pressure within it rises to about 80 or 100 mm. of water. But after the corresponding sciatic nerve is cut, the increased afflux of blood resulting from the vasodilatation elevates the pressure in the occluded femoral vein to 280 mm. of water Cutting the sciatic nerve thus serves to increase the venous pressure, which indicates that the capillary pressure is also elevated Hence, the result of Ranvier's experiment is in excellent accord with the explanation of edema in venous occlusion as a result of increased capillary pressure. Moreover, Cohnheim and Sotnitschewsky[6] showed that if the veins of the hind limbs of a dog be completely occluded with plaster of Paris, edema develops without the necessity of dividing the sciatic nerve. These experiments fully justify Cohnheim's conclusion that "it is indubitable that the fluid of edema is expressed from the capillaries and smallest veins as the result of a rise of pressure proceeding from the venous side."

In such experiments on the production of edema by constriction of an extremity, the impediment to lymphatic drainage is doubtless also significant. It has long[7] been known that when the venous return from a limb is obstructed, there is a great increase in the amount of lymph formed. In constriction experiments, this compensation for venous obstruction is, of course, inhibited. But the same is quite possibly true in human cardiac failure with venous engorgement. The increased venous pressure may offer added resistance to the emptying of the lymph into the venous system and thus produce corresponding stagnation in the lymphatics

In recent years, several quantitative studies have been carried out on the production of edema in humans by constriction of an extremity. Mende[31] found that such constriction results in pitting edema when the volume of the extremity has been increased 10 per cent; Drury and Jones[11] observed this figure to be about 8 per cent. They noted that the rate at which edema is produced by such constriction increases as the venous pressure is raised, and that the rate of transudation gradually declines as edema collects in the limb. Similar studies were carried out by Krogh, Landis and Turner,[24] who used a pressure plethysmograph which compressed the blood vessels and thus permitted the accurate determination of small changes in tissue volume They found that fluid accumulates in the tissue spaces when the constriction elevates the venous

pressure above 15 or 20 cm. of water. Above a venous pressure of 17 cm. of water, the rate of filtration is directly proportional to the increase in venous pressure. They further found that when the colloid osmotic pressure of the blood is elevated by standing,* the rate of filtration produced by a given venous pressure is lower.

Rôle of Increased Capillary Pressure in Cardiac Edema.—In the foregoing, it has been seen that clinical observation demonstrates the close correlation of cardiac edema with venous stasis. It has also been seen that edema can be produced experimentally, both in animals and man, by adequate venous obstruction. The next question that arises concerns the mechanism through which venous stasis produces edema. Available evidence seems to speak strongly in favor of the following conception: As a result of venous stasis, the venous pressure is increased The venous hypertension results in an increase in the hydrostatic pressure in the capillaries This capillary hypertension displaces the equilibrium between the hydrostatic pressure in the capillaries and the colloid osmotic pressure so that filtration is increased and resorption diminished, the result of which is edema That increase in capillary pressure has this consequence has been proved directly by the beautiful experiments of Landis[25] on the frog's mesentery. He showed that when the hydrostatic pressure in a capillary was elevated above the colloid osmotic pressure of the blood, transudation occurred. According to this conception, then, *cardiac edema is primarily a symptom of capillary hypertension.* Strongly in favor of this view is the abovementioned finding of Drury and Jones and Krogh, Landis and Turner that when the venous return from the limb is impeded by constriction, the rate of formation of edema is proportional to the venous pressure

The theory that cardiac edema results primarily from increased hydrostatic pressure in the capillaries thus seems very probable. In accord with this conception, Mueller[32] and others observed with the capillary microscope that the venous limb of the capillaries is dilated in cardiac failure with venous engorgement. However, until lately the increased capillary pressure in right heart failure was not unequivocally demonstrated by direct measurement. It is true that von Basch,[47] Liebesny[28] and others found the capillary pressure elevated in heart failure, but this was not the case in most of the cases studied by Boas and Dooneief.[4] These investigators used indirect methods of uncertain reliability[12] so the disagreement is not surprising. Recently, Fahr and Ershler[17] have filled the gap by measuring the capillary pressure in right heart failure by Landis' direct technic of introducing a very fine glass cannula directly

* Thompson *et al* [44] have shown that protracted standing increases the concentration of the blood, and consequently the colloid osmotic pressure, evidently as a result of transudation of protein-poor fluid into the lower extremities

into the blood capillary. They found that while normally the pressure in the venous end of the cutaneous capillary loops averages 12 mm.Hg in 5 patients with edema due to right heart failure this pressure was between 25 and 41 mm. In one of their patients improvement of the right heart failure was accompanied by fall in capillary pressure from 25 to 12 mm These observations lend strong support to the theory that increased hydrostatic pressure in the capillaries is concerned in the genesis of cardiac edema.

It should be mentioned that the theory here supported, that capillary hypertension is the fundamental cause of cardiac edema, is not universally accepted. For a detailed exposition of the arguments against it, the reader is referred to Volhard's[46] monograph. He believes that the essential factor in producing cardiac edema is not increased capillary pressure but rather injury to the capillaries due to the asphyxia of the tissues produced by circulatory retardation. That increase in capillary permeability is at most a secondary factor in the genesis of cardiac edema will be seen below.

The Colloid Osmotic Pressure of the Plasma and Cardiac Edema. —Epstein,[14] Rowe,[38] Payne and Peters,[33] Thomson,[45] and others have found that the protein content of the blood plasma is often, though by no means always, diminished in patients with cardiac insufficiency. This is especially often the case when the heart failure is of *protracted duration, when edema appears soon after the* onset of heart failure, I have repeatedly observed normal concentration of plasma proteins The diminution affects the albumin fraction either exclusively or much more than the globulins The decrease in albumin content entails a corresponding diminution in the colloid osmotic pressure of the plasma, which has also been demonstrated by direct measurements of colloid osmotic pressure carried out by Iversen and Nakazawa[21] Payne and Peters found that the decrease in protein content of the plasma paralleled the nutritional state of the patient, and therefore attribute the former to malnutrition, largely on the basis of anorexia and sometimes also vomiting. Some cardiacs lose considerable protein in the urine over protracted periods, which may be significant, especially if engorgement of the liver interferes with the regeneration of the lost protein; there is some, though not conclusive, evidence that the plasma proteins are produced in the liver The restricted diet on which most cardiac patients are kept may also contribute to hypoproteinemia. The same is true of patients with ascites or hydrothorax who are repeatedly tapped, and thereby lose protein.

It would seem very probable that diminished colloid osmotic pressure of the plasma in cardiac failure often plays an accessory rôle in favoring the development of edema. We have cited above the findings of Krogh, Landis and Turner that diminution in colloid osmotic *pressure increases the rate of edema formation in experi-*

mental venous stasis, the same is doubtless true in human right heart failure. However, hypoproteinemia cannot be the essential factor in cardiac edema for it is sometimes absent and is rarely marked enough to explain in itself the transudation.

The Permeability of the Capillaries in Cardiac Edema.—There is considerable evidence to show that in health the subcutaneous capillaries are almost impermeable to protein. However, it has been found that if the capillaries are damaged by arsenic, alcohol, or various other poisons, they become permeable to protein. Of significance in the present connection is the finding of Landis[25] that capillaries are rendered permeable to protein by oxygen deprivation of three minutes' duration.

It has been thought that circulatory failure damages the capillaries, and some have endeavored to explain cardiac edema on this basis. It is true that under the conditions in which cardiac edema occurs, the permeability of the capillaries in the edematous area is increased. This is indicated by the protein content of the edema fluid, which is generally about 0.2 to 0.5 per cent, and especially that of the effusions into the serous cavities, which may reach 3 per cent or more. It is quite plausible, though not proved, that the increase in permeability is a consequence of defective nutrition of the capillaries resulting from slowing of blood flow through them. When marked arterial anoxemia is present as a result of pulmonary changes, this may also contribute. Another possibility that must be considered is that the increased permeability to protein is due to the dilatation of the venous ends of the capillaries that is present in venous stasis; Krogh[23] has brought evidence that under certain circumstances capillary dilatation increases the permeability.

Nevertheless, it scarcely seems probable that the increased permeability of capillaries is more than an accessory cause of cardiac edema. The protein content of the edema fluid, generally less than 0.5 per cent, does not indicate a very striking increase in permeability. According to Starling's theory, the way in which increased permeability of the capillaries to protein favors edema would seem to be as follows: Under normal circumstances the plasma contains about 7 per cent of protein and the intercellular tissue fluid practically none. The hydrostatic pressure in the capillaries is therefore opposed by the colloid osmotic pressure of 7 per cent of protein. But if the capillaries are so permeable to protein that the tissue fluid contains 3 per cent of protein, this partially counterbalances the plasma protein so that the hydrostatic pressure is opposed by the colloids osmotic pressure of only $7 - 3 = 4$ per cent of protein and edema would probably result. Since in cardiac dropsy, the subcutaneous edema contains not 3 but less than 0.5, and sometimes less than 0.2, per cent of protein, it would seem that this

factor can be quantitatively of but little significance in producing subcutaneous edema. But in the case of ascites and hydrothorax, which may contain 2 or 3 per cent of protein, the increased capillary permeability may be a very important factor This is probably especially true in long-standing effusions which recur repeatedly after tapping, although the subcutaneous edema has cleared up; in such effusions, the protein content is usually very high.

Summary.—Cardiac edema (other than pulmonary) occurs in right heart failure and in hypodiastolic failure, but not in insufficiency of the left heart or the peripheral circulatory failure of shock This occurrence of cardiac edema indicates that it results from venous engorgement. There is much evidence showing that venous engorgement produces edema primarily through the intermediacy of increased hydrostatic pressure in the capillaries Accessory factors in the pathogenesis of cardiac edema are increased permeability of the capillaries to protein and decrease in the colloid osmotic pressure of the plasma. It would seem that the factor of increased capillary permeability is more significant in the pathogenesis of effusions into the serous sacs than of subcutaneous edema The absence of peripheral edema in left heart failure and the peripheral circulatory failure of shock shows that diminution of blood flow *per se*, and without increased capillary pressure, does not produce edema

SEROUS EFFUSIONS

The picture of cardiac dropsy often includes effusion into the serous sacs. In fact, while not the rule, it is not uncommon for a serous effusion to antedate subcutaneous edema, which may not develop at all. This is especially true of hydrothorax; roentgen examination reveals that quite often small, or more rarely large, pleural effusion is the only evidence of transudation due to heart failure Fluid may reaccumulate repeatedly in the pleural cavity as a result of heart failure although anasarca is at no time demonstrable While ascites may also develop in the absence of anasarca, this is uncommon apart from instances of constructive pericarditis or complication by severe hepatic changes. Predominance of ascites over other dropsical manifestations has seemed to me more common in childhood, perhaps because of greater frequency of clinically occult pericardial involvement at this age At necropsy of individuals succumbing to heart failure, the volume of fluid in the pericardium is generally increased, but significant hydropericardium seems to be a rarity. The volume of cerebrospinal fluid is apparently not increased (page 277). Nor have I seen hydrarthrosis purely as a result of heart failure. When cardiac dropsy is absorbed, the serous effusions usually outlast the anasarca

HYDROTHORAX

It is an interesting and long-known fact that cardiac hydrothorax is often unequal on the two sides, usually predominating on the right. The following statistics regarding this point are given by Steele.[41] The pleural effusions were unequal on the two sides in three-fourths of 75 patients with hydrothorax due to heart failure. In one-fifth of the cases, the effusion was unilateral. Of the unequal effusions, the larger was on the right side in three-fourths of the cases, while of 13 unilateral effusions, 10 were on the right side. Similar findings have been recorded by Stengel[42] and others Steele noticed that predominance of right hydrothorax tends to occur with greater enlargement of the right heart, while in 9 of 11 instances of left-sided effusion, the left heart was especially enlarged. Unilateral cardiac hydrothorax often recurs repeatedly after aspiration without effusion into the other pleura, it has been said (Gerhardt, cited by Matthes[30]) that this occurs especially in older individuals, which is in accord with what I have seen

Not only is cardiac hydrothorax not uncommonly unilateral, but on rare occasions it is *encapsulated*, either in the general pleural cavity or in an interlobar fissure Instances of encapsulated hydrothorax in heart failure have been reported by Stewart,[43] Kiser,[22] and Austrian;[1] I have seen two such cases recently in which diagnostic difficulties were at first encountered The dependence of these interlobar effusions on heart failure is shown by the nature of the fluid obtained on aspiration and particularly by the fact that they clear up with improvement of the heart. The encapsulation of cardiac hydrothorax results from pre-existent pleural adhesions Pleural adhesions themselves may swell greatly as a result of edema due to heart failure and cause roentgen shadows at the periphery of the lung field which may be difficult to interpret correctly (Zdansky[50]).

The *fluid* in cardiac effusions is generally of a pale straw color but may be a deeper yellow or amber. Usually, it is clear and shows no tendency to clotting, but long-standing effusions may be somewhat cloudy and even contain flakes of fibrin. Complication by infarction of the lung may render the fluid bloody. Otherwise, a sanguineous appearance is accidental and a result of the puncture.

Regarding the protein content (for determinations of the colloid osmotic pressure see Iversen and Nakazawa[21]) and specific gravity, which is determined predominantly by the protein content, the following average figures have been collated by Dickinson[10] from a large number of cases of heart disease studied by himself and others:

	Specific gravity	Protein content, per cent
Pleura	1 013	2 11
Peritoneum . . .	1.014	2 34
Pericardium . . .	1 018	3 08
Anasarca fluid . . .	1.008	0 35

It is thus seen that the protein content of the serous transudates in heart failure—as in other forms of transudation—is much higher than that of the subcutaneous edema fluid. It is also higher than that of serous effusions in nephrotic dropsy (Epstein[16]). Evidently, the processes leading to the formation of transudates in serous cavities as a result of heart failure are accompanied by relatively high permeability to protein of the capillaries of the serous membranes. The result is that the protein content of the cardiac transudates tends to approach that of inflammatory exudates. This is especially often the case in long-standing effusions which have been tapped repeatedly; here, of course, it is possible that the increased protein content is actually the result of secondary inflammatory processes. It is widely accepted that specific gravity of 1 018 or more and protein content of over 4 per cent indicate the inflammatory nature of an effusion But there are also instances of definitely inflammatory exudate (*e g*, in tuberculous pleurisy) with somewhat lower specific gravity and protein content. The result is that not uncommonly one encounters borderline cases with specific gravity between about 1.013 and 1 019 in which it cannot be stated from this criterion alone whether an effusion in a patient with heart disease is a transudate resulting from cardiac failure or is of inflammatory origin I have several times had this difficulty in pleural effusions in patients with active rheumatic fever and *cardiac insufficiency* Usually, if one adds a few drops of glacial acetic acid to an exudate, a cloud appears which redissolves in an excess of acid, while the cloud does not appear in transudates. But I have not found that this or any of the other similar "tests" afford more information than does the simple determination of the specific gravity.

Cytologically, it was long ago pointed out by Widal and Ravaut[49] that cardiac effusions contain a large number of endothelial cells. These are often present in plaques In transudates of considerable standing, notably in bloody hydrothorax when pulmonary infarction complicates heart failure, these cells may closely simulate those of mesothelioma of the pleura, in a recent case of this nature, malignant disease was strongly suspected by a competent pathologist on the basis of the cytology of the pleural fluid There are often also a considerable number of lymphocytes, and red blood cells may be abundant. As a rule, polymorphonuclear leukocytes are not prominent, but these are exceptions to this rule, especially when there is also pulmonary infarction, consequently, this criterion for differentiation from inflammatory exudation is not infallible.

The development of hydrothorax usually aggravates the symptoms of heart failure which are already present, especially dyspnea. This is probably largely due to displacement of the heart with kinking of the great veins, but with large effusions the compression

of the pulmonary parenchyma may also be significant. It should be remembered that if a pleural effusion in an adult is demonstrable by physical examination, 500 cc or more are generally present, and removal of little more than this amount often affords marked relief. For this reason, the early detection of hydrothorax in cardiac patients is important The physical and roentgen signs of cardiac hydrothorax do not differ from those of pleurisy with effusion except that mobility of the upper border of the fluid is more often demonstrable in hydrothorax because limitation of the fluid by pleural adhesions is less often present than in inflammatory disease.

Pathogenesis.—The mechanisms leading to transudation into the tissue spaces and serous cavities in heart disease have already been discussed (page 192). However, while hydrothorax most often occurs in the presence of subcutaneous edema, this is not invariably the case, and either may be found in the absence of the other. It is therefore evident that in addition to the general pathogenetic factors resulting in cardiac dropsy, there must be additional, local mechanisms favoring or inhibiting transudation into the pleura. This is also indicated by the fact that cardiac hydrothorax may be unilateral and is most often unequal on the two sides

The venous drainage of the pleura is into both the superior vena cava and the pulmonary veins This anatomical peculiarity suggests that either right or left heart failure may tend to raise the pressure in the pleural veins and capillaries and thus favor the occurrence of hydrothorax. However, hydrothorax does not occur in isolated failure of the left heart even when the latter is severe enough to lead to pulmonary edema; apparently, the venous return through the channels which empty into the azygos veins and then into the superior vena cava and right heart is adequate to prevent passive engorgement of the pleura sufficient to produce hydrothorax. Similarly, I have seen several instances of pure right heart failure in which hydrothorax did not appear although there was massive peripheral edema and even ascites In these cases, it seems plausible to believe that the venous return into the pulmonary veins and left heart sufficed to prevent transudation into the pleura. However, that *complete* obstruction of the azygos major vein suffices *per se* to produce hydrothorax is shown by West's[48] case, in which thrombosis of this vessel resulted in recurrent right hydrothorax But in the production of cardiac hydrothorax it would seem that insufficiency of both the right and the left sides of the heart with resultant engorgement of both the superior vena cava and pulmonary veins is usually prerequisite. In this respect, cardiac hydrothorax differs from peripheral edema, which is correlated almost solely with engorgement of the systemic veins.

There have been a number of attempts to explain the predominance of right-sided hydrothorax in heart failure. The most widely

held view was first advanced by Baccelli[2] in 1863, and has since been widely accepted with various modifications He thought that the increased weight of the enlarged right heart carries the superior vena cava downward and with it the vena azygos major. This would draw the latter vein tightly around the root of the right lung and thus compress it. Since then, other investigators have thought of direct compression of the vena azygos major against the root of the right lung by the dilated right heart, the view favored by Steele and Stengel Against this theory, however, Fetterolf and Norris[18] point out that it is anatomically impossible for the heart, either directly or indirectly, to exert pressure on the azygos major vein Fetterolf and Norris believe that the right-sided effusions are due to compression of the right *pulmonary* veins in the root of the lung by the dilated right auricle, and the left-sided effusions are similarly due to compression of the left pulmonary veins by the dilated left auricle. But it would seem that the usual *absence of pulmonary edema in patients with cardiac hydrothorax* speaks against this theory, as does the converse fact that pulmonary edema resulting from hypertension of the lesser circulation in left heart failure is generally not accompanied by pleural effusion. It has also been thought that the presence of an enlarged liver may interfere with the respiratory movements of the right chest and thereby tend to hamper the absorption of fluid from that side. Another factor considered by West is that the predominance of the effusion is determined by which side the patient lies on. While it is probably true that lying on one side will increase the effusion there, it scarcely seems that this can be the sole explanation, I have seen right-sided effusions in which the patient reclined mostly on the left side Actually, I believe that the usual sequence of events is that the effusion first forms and then the patient prefers to lie on this side because it does not interfere with the movements of the uncompressed lung Recently, Satke[39] has found that in 7 of 8 healthy persons, the negative pressure was greater in the right pleural cavity than in the left, while in the remaining individual the pressure was practically the same on both sides. He believes that this fact explains the predominance of right-sided effusions. But it does not explain the left-sided effusions All in all, it would seem that the causes of unequal pleural effusion in heart failure have not yet been elucidated.

ASCITES

Ascites occurs in those forms of heart failure which produce systemic venous engorgement, *i e.*, right heart failure and hypodiastolic failure. The ascites of the latter is discussed on page 610. Here it will merely be remarked that recurrent ascites, simulating

that of mediastino-pericarditis, may occur in right heart failure due either to rheumatic or arteriosclerotic heart disease, and I have also seen it on rare occasions in syphilitic heart disease. The patients have usually had a protracted period of right heart failure with long-standing engorgement of the liver, the hepatic changes may well be concerned in the occasional predominance of the ascites over the subcutaneous edema and hydrothorax.

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CHAPTER XIII

THE LUNGS: I. PULMONARY ENGORGEMENT

A LARGE part of the symptomatology of heart failure is directly attributable to passive engorgement of the lungs Indeed, so completely may pulmonary symptoms dominate the clinical picture of heart failure that one is not uncommonly in doubt whether a dyspneic and cyanotic patient is suffering from primary disease of the heart or of the lungs The shortness of breath which generally first signals the onset of heart failure is a manifestation of pulmonary engorgement (page 121) The *rationale* of the usual predominance of symptoms of congestion of the lungs is obvious: the common forms of heart failure—those resulting from hypertension, coronary arteriosclerosis, and mitral and aortic valvular defects—are initiated as insufficiency of the left side of the heart, of which pulmonary engorgement is an inevitable consequence Throughout the entire course of heart failure, pulmonary manifestations constitute an omnipresent danger, and in most instances of cardiac disease the end is ushered in by morbid processes in the lungs

In the following, we shall first describe passive engorgement of the lungs, and then its three main complications—edema of the lungs, pulmonary infarction, and bronchopneumonia.

PATHOGENESIS OF PULMONARY ENGORGEMENT

Passive engorgement of the lungs results from failure of the left side of the heart which is not accompanied by equally severe functional depression of the right ventricle. The reasons why pulmonary engorgement develops under these circumstances are inherent in the mechanism regulating the lesser circulation For this reason, we shall discuss first the regulation of blood flow through the lungs in health

The Regulation of the Pulmonary Circuit.—Contrary to the state of affairs in the systemic circuit, the chemical and nervous control of the caliber of the small pulmonary vessels, while it exists, is of secondary significance in regulating the volume of flow through the lungs In the greater circulation, such chemical and nervous regulation having its site of action in the small peripheral vessels is indispensable because it is the only means by which blood can be diverted from a resting organ to one which is active at the time and therefore needs a larger portion of the cardiac output. In the lungs, on the contrary, such collateral differentiation* is hardly

* Whether those parts of the lungs which are most actively ventilated receive a more copious blood supply remains to be determined But even if such is actually the case, the regulation may well be accomplished through the facilitation of blood flow by the more ample respiratory excursions in the more active parts of the lungs

needed, for the different parts are functionally equivalent. It is therefore not surprising that a number of investigators (see Wiggers[31] for summary) have established that *the volume of blood flow through the lungs is determined primarily by the activity of the heart,* and that in health variations in the resistance in the lungs are of little moment. Histological studies have shown that the caliber of the arterioles (the main factor in the resistance to blood flow) in the lungs is much greater than in the systemic circuit, according to the measurements of Miller[17] the precapillary arteries of the lung have a mean diameter of 80 microns, while that of the corresponding vessels of the greater circulation is but 10 or 15 microns The capillaries of the lung are also very wide. The blood consequently encounters little resistance and flows rapidly through the lungs despite the fact that the mean pressure in the pulmonary artery is probably only of the order of 25 mm. of mercury Further, the studies of Hall,[9] Toyama[29] and others have shown that, as in other organs, there are many "reserve" capillaries which are opened when blood flow is increased. And in most conditions of heightened blood flow, the depth of respiration is increased, with resultant augmentation in the average cross-section of the pulmonary capillary bed due to the distention of the lungs. The consequence of these arrangements is that, in health, any volume of blood which is returned to the right heart from the great veins is readily pumped through the lungs, apparently with comparatively little rise of pressure in the pulmonary artery.

Further, the efficiency of the healthy left heart is so great that it is readily able to master the volume of blood that is pumped through the lungs and thus avert stasis in the pulmonary veins; the pressure in the latter oscillates around atmospheric—rising above during expiration and falling below during inspiration—even when the volume of blood flow through the lungs is very great This accommodation of the activity of the left heart to the volume of blood flow through the lungs is effected through the mechanism expressed in Starling's law of the heart (page 302) and has been beautifully illustrated by Henderson and Prince.[10] Working with the perfused cat's heart, they measured the effect of change in filling pressure on the individual output of each ventricle Henderson and Prince found that when the filling pressure is below 5 cm. of water, the output of the right ventricle is greater than that of the left, which would tend to cause blood to accumulate in the lungs and thus prevent undue depletion of the pulmonary circuit under conditions of small venous return to the right heart. Between 5 and 8 cm. filling pressure, the outputs of the ventricles are approximately equal, which would maintain the blood content of the lungs close to a constant level. It will be noted that these filling pressures correspond to those present in the healthy resting individual; for

and Weiss[9] found that in patients with left ventricular failure, the slowing of blood flow is *largely in the pulmonary circuit. Using* the saccharin method, Hitzig, King and the writer[11] found that the velocity of blood flow through the lungs is prolonged in the vast majority of patients with symptoms of insufficiency of the left heart. In such patients, the arm-to-tongue circulation time is often triple the normal, despite normal pressure in the antecubital vein, indicating functional competence of the right side of the heart. In a number of cases of early left ventricular failure, we found that while the arm-to-tongue circulation time measured with saccharin was prolonged, the arm-to-lung circulation time measured with ether (page 52) was normal. This finding shows that in the cases in question the slowing of blood flow was in the venous half of the pulmonary circuit, *i. e.*, the portion *downstream* to the arterial capillaries of the lung. Since the velocity of flow is inversely proportional to the cross-section of the stream bed, the slowing of flow in the venous half of the pulmonary circuit indicates that in initial left heart failure the excess of blood above the normal contained in the pulmonary circuit is accommodated in the venous half of the circuit.

In exceptional instances of otherwise typical left heart failure with severe orthopnea and dyspnea, Hitzig, King and the writer found the pulmonary circulation time normal. In such cases, it is to be presumed that the right ventricle increases the force of its contractions sufficiently to propel the blood through the pulmonary circuit at a normal velocity, despite the increased resistance due to the elevation of the diastolic pressure within the failing left heart. However, this is accomplished only by the maintenance of higher pressure within the pulmonary vessels, which results in the dyspnea, hemoptysis and other symptoms from which such patients suffer.

PATHOLOGICAL ANATOMY OF PULMONARY ENGORGEMENT

When the chest is opened, engorged lungs do not collapse as much as normal organs. They are rather heavy, of increased consistency, cut with more resistance than usual, and while crepitation is present it is generally less than in an unchanged lung. If the engorgement is of relatively recent inception, the cut section is most often predominantly red in color (red induration). When the stasis has been present for a considerable time, the section presents a characteristic brown or rusty brown color (brown induration) which becomes red on standing. Often, hemorrhages and infarcts in various stages of evolution or resolution are present. In many intensely engorged lungs, squeezing or scraping the surface with the knife reveals no edema, but in others abundant, more or less bloody and frothy fluid can be expressed. In long-standing

cases, the small arteries may stand out because of their thickened walls and the larger ones may have patches of atheroma. The walls of the bronchi are dark red and often thickened; the lumens generally contain thick mucus which is often bloody and may be purulent.

Microscopically, the outstanding feature is the intense engorgement of the wide and tortuous capillaries which protrude bud-like far into the alveoli and often diminish the air space notably. The alveoli contain red blood cells in varying numbers, often many desquamated alveolar epithelia, and generally some leukocytes The characteristic cellular element, however, is the so-called heart failure cell, which is found not only in the alveoli but in smaller numbers often also in the interalveolar septa as well as rarely in the capillaries and lymph spaces. Sometimes, these cells are so numerous as almost to fill many alveoli They may be found in great numbers in the vicinity of old hemorrhages and infarcts. Heart failure cells are large mononuclear elements characterized by the presence in the cytoplasm of pigment granules, revealed by iron stains to be hemosiderin The pigment emanates from the hemoglobin of extravasated red corpuscles, which disintegrate and are taken up by the phagocytic cells. The origin of heart failure cells has been much disputed, they have been regarded as histiocytes, as monocytes from the circulating blood, and as alveolar epithelia. It seems plausible that all these varieties of cells may assume phagocytic properties and take up the detritus of the erythrocytes.

In long-standing pulmonary engorgement, moderate hyperplasia of the collagenous framework may occur Hyperplasia of the reticulum, elastic and muscle fibers has also been described Areas of atelectasis and of bronchopneumonia are almost always to be found, and not uncommonly there is considerable emphysema. Corpora amylacea are not rare in the engorged lung, they have been attributed to agglutinated and hyalinized masses of red cells.

Hypostatic Congestion.—Pulmonary hypostasis is a variety of pulmonary engorgement that may develop when circulatory failure is accompanied by weakness of the respiratory movements. It is especially apt to occur in the debilitated, the old, the comatose, and those who because of disease of the central nervous system are *constrained to remain in one position The respiratory movements* furnish considerable aid in the maintenance of the pulmonary circulation, although they are not indispensable when the heart is vigorous. But when the left heart is failing, weakness of the respiratory movements favors accumulation of blood in the dependent parts of the lung, where the blood must overcome the force of gravity to return to the left heart Since the patients are bedridden, hypostatic congestion occurs especially in the posterior

parts of the lower lobes The distribution of the engorgement is affected by the position in which the patient lies, and in hemiplegia may be largely on the paralyzed side. The affected lobes are heavy and of a dark red, sometimes almost black color. Considerable *portions are atelectatic, not having been adequately ventilated* by the feeble respiratory movements Areas of hypostatic congestion are often edematous, their appearance may resemble that of the spleen (splenization) As a rule, areas of bronchopneumonia are present in lungs that are the seat of hypostatic congestion.

CLINICAL PICTURE OF PULMONARY ENGORGEMENT

Passive engorgement of the lungs is only one of the consequences of failure of the left heart. For this reason, the symptoms due to pulmonary congestion are often commingled with other results of weakness of the left heart, and are generally joined sooner or later by systemic venous engorgement, swelling of the liver, peripheral edema, and other evidences of failure of the right heart. Nevertheless, there are many instances of insufficiency of the left heart in which the symptoms are almost exclusively those of pulmonary engorgement. Such patients, especially when elderly, are often mistakenly considered to suffer from primary pulmonary or bronchial disease, notably emphysema, fibroid phthisis, bronchial asthma, carcinoma, or the much-abused chronic bronchitis In the young, when cough and hemoptysis are outstanding symptoms, mitral stenosis is not rarely confused with pulmonary tuberculosis and the victim sent to a sanatorium.

Dyspnea.—Exertional and paroxysmal dyspnea are the most common symptoms of pulmonary engorgement and usually bring the patient to the physician. They are generally accompanied by *orthopnea*. However, it should be mentioned that there are instances of marked pulmonary engorgement in which the patient does not complain spontaneously of dyspnea and must be questioned directly to elicit its existence I have several times seen individuals with mitral stenosis in whom pulmonary engorgement was demonstrable on radiographic examination, yet who claimed that they were hardly, if at all, short of breath. In such instances, hemoptysis may be the only symptom of pulmonary engorgement. Despite these exceptions, it is to be emphasized that pulmonary engorgement in the absence of dyspnea is very rare. As has already been mentioned, when the right heart fails in a patient with pulmonary engorgement, dyspnea may diminish *pari passu* with increase in systemic venous engorgement, edema and swelling of the liver. The pathogenetic relations of pulmonary engorgement and dyspnea are considered in detail in Chapter VII

Cyanosis—Cyanosis is another common symptom of passive congestion of the lungs, but is not nearly as constant as dyspnea The development of very deep cyanosis other than terminally generally bespeaks some complication, notably massive pulmonary edema or infarction, bronchopneumonia, or pleural effusion. Of course, when pulmonary engorgement supervenes in emphysema, fibroid phthisis or congenital heart disease, the cyanosis may be very deep. In patients with engorged lungs, dyspnea and cyanosis do not always run parallel Thus, when the right heart fails in such individuals, cyanosis may deepen as dyspnea and orthopnea are alleviated. The relations of cyanosis to pulmonary engorgement are further discussed in Chapter XI.

Cough—Cough is frequently, but by no means always, present. Since cough is not provoked by changes in the lung tissue *per se*, it is to be presumed that pulmonary engorgement results in cough only when the transudate in the alveoli is sufficiently abundant to reach the larger bronchi, from which the cough reflex can be initiated. A much more important factor in producing the cough of pulmonary engorgement seems to be congestion of the bronchial mucous membrane. It will be remembered that the veins supplying the small bronchi anastomose freely with the pulmonary veins, and that the bronchial veins drain partially into the latter The result is that the bronchi are inevitably implicated in pulmonary engorgement due to left heart failure Moreover, inasmuch as another and larger part of the bronchial venous drainage, especially from the larger bronchi, is into the systemic veins, the bronchi also become engorged as a result of right heart failure Passive *congestion of the bronchi is thus a consequence of both left and* right heart failure. Engorgement of the bronchial mucous membrane results not only in swelling but also in a desquamative catarrh, the lumen containing mucus and cellular elements Moreover, there is often also a secondary infectious element in the bronchial catarrh, as evidenced by purulent admixture in the otherwise mucous expectoration. The resulting cough is very severe in many instances, and in some it is the outstanding symptom Especially the latter type of case, occurring in elderly persons, frequently goes unrecognized for a long time and is treated for bronchitis The cough may be worse at night, or present exclusively at this time There is also a variety of nocturnal cough in patients with engorged lungs which is to be regarded as an "equivalent" of cardiac asthma, and which may be associated or alternate with paroxysms of nocturnal dyspnea (page 147). In other patients, paroxysms of cough are incited by exertion In every elderly person with a protracted cough, even though it is a "winter cough" clearing up with warm weather, the possibility of cardiac origin should be borne in mind.

The cough that is associated with such complications of pulmonary engorgement as infarction of the lung, massive pulmonary edema and bronchopneumonia will be discussed in connection with these conditions. A paroxysm of cough may precede the appearance of the blood in hemoptysis or the characteristic expectoration in pulmonary edema On rare occasions, severe paroxysmal cough results from pressure on the primary bronchi by the dilated left auricle in mitral stenosis (page 506) Another rare mechanism of cough in left heart failure is that sometimes associated with the onset of hoarseness in left recurrent laryngeal paralysis due to compression of the nerve by the dilated pulmonary artery (page 507); usually, the cough soon clears up although the patient remains hoarse.

In elderly patients with both emphysema and arteriosclerotic heart disease, one is not uncommonly in doubt whether cough is due to chronic bronchitis correlated with the emphysema or to pulmonary engorgement due to left heart failure. The decision is naturally significant for the line of therapy to be followed. In several cases that I have followed, it has seemed to me that cough due primarily to the pulmonary and bronchial engorgement of left heart failure has in turn resulted in a considerable degree of emphysema. The development of emphysema in protracted pulmonary engorgement is presumably also favored by the tendency of the dyspneic cardiac patient to hold his chest in a relatively "inspiratory" position as a result of the disturbance in respiratory mechanics (page 222). The development of emphysema in chronic pulmonary engorgement throws a further strain on the right heart, a vicious circle being established

Another similar dilemma is not rare in syphilitic aortitis, in which cough and dyspnea may be due either to pressure on the left bronchus by the dilated aorta or to left ventricular failure consequent on aortic insufficiency

In the determination whether cough is due to pulmonary engorgement or to some other cause, measurement of the arm-to-tongue circulation time is often of great aid; it is almost always prolonged in left heart failure, and normal in such conditions as emphysema or aortic aneurysm without heart failure

Expectoration.—While the cough may be unproductive, more often it is accompanied by expectoration. This is generally mucous in character, but becomes purulent when there is secondary infectious bronchitis. The sputum frequently contains points, threads or streaks of blood. As a result of its content in hemosiderin, free or in heart failure cells, the sputum is often brownish in color The entire sputum may be thus discolored or there may be brownish dots or streaks in an otherwise clear medium. Even in the absence of demonstrable infarction, the sputum may be diffusely and deeply bloody or resemble the rusty sputum of pneumonia. Microscopi-

cally, the characteristic, though not constant, feature is the presence of the heart failure cells described above. These cells are best sought in the brownish bits of mucus, if these are present. They appear as relatively large elements from the size of a polymorphonuclear leukocyte to several times as big The cytoplasm contains yellowish-brown or almost black hemosiderin pigment most often in the form of granules, but sometimes diffusely distributed through the cell body. These cells can often be recognized in the unstained smear. However, they are more readily demonstrated by staining with 10 per cent solution of potassium ferrocyanide and dilute hydrochloric acid, and then warming a little; the iron-containing pigment is stained blue. It should be remembered that these pigment-containing cells are not specific for pulmonary engorgement, they may be present in any variety of pulmonary bleeding that has occurred long enough prior to the examination to allow for the formation of hemosiderin from hemoglobin Nevertheless, the presence of large numbers of heart failure cells in the sputum is sometimes of decided aid in differentiating pulmonary engorgement from emphysema and other conditions The search for heart failure cells is a diagnostic aid that has been too little used since the roentgen era. Heart failure cells should not be confused with the black carbon containing cells that are present in pneumokoniosis and in small numbers in the morning expectoration of many city dwellers

The sputum in pulmonary engorgement, even in the absence of frank edema of the lungs, often contains considerable quantities of protein; in this, it differs from the expectoration in most instances of chronic bronchitis associated with asthma or emphysema.

Hemoptysis.—Hemoptysis is another common symptom of pulmonary engorgement It is true that many patients with protracted and severe pulmonary engorgement never expectorate blood. But in others the sputum contains blood for weeks or months at a time. Most often, the pulmonary bleeding is but slight and evinced only by points or streaks of blood in the sputum. Rarely, the expectoration consists largely of blood despite the absence of other indications of pulmonary infarction The blood may be of various shades, from bright red to almost black, fluid or partly clotted.

Important, though unusual, are the instances of hemoptysis in pulmonary engorgement in which the bleeding is so profuse as to seem immediately threatening to life. These patients are sometimes mistakenly considered to suffer from pulmonary tuberculosis. I have only once seen death due to exsanguination as a result of the hemoptysis of pulmonary engorgement. This was in a girl, aged eighteen years, who had been under my care for some years; she had hemoptysis of a pint or more on several occasions prior to the fatal hemorrhage, transfusion being necessary on two occasions

These massive hemoptyses may come on suddenly while the patient feels relatively well and is up and about. Sometimes, there is no obvious exciting cause, but in other instances they seem to have been precipitated by physical exertion or a psychic trauma (Duken,[8] Oppenheimer and Schwartz[20]), both of which increase the venous return to the heart and therefore the degree of pulmonary engorgement when the left heart is insufficient For an excellent description of the clinical phenomena of massive hemoptysis in heart failure, the reader is referred to the study of Oppenheimer and Schwartz

The pathogenesis of hemoptysis in pulmonary engorgement is not always the same. There seem to be two main origins of the blood in the sputum, both of which are often combined in the same patient·

1. Large or small hemorrhagic infarcts of the lung are a common source of blood-streaked sputum or more massive hemoptysis in pulmonary engorgement. They are discussed in detail on page 241, but here it may be remarked that hemoptysis may be the only clinical evidence of pulmonary infarction in heart disease.

2. Foci of hemorrhage into the lung which are not the result of infarction, the so-called pulmonary apoplexy Such areas are almost always present in engorged lungs and may be very numerous. It seems probable that most of these foci of pulmonary bleeding are the result of diapedesis from the distended and dilated capillaries which project so prominently into the alveoli; the frequency of actual rupture remains to be demonstrated. The underlying cause of the capillary distention and therefore of the bleeding is doubtless the high blood pressure within the vessels, the hemoptysis is thus a symptom of hypertension of the lesser circulation. It is for this reason that blood spitting often occurs in patients with mitral stenosis who have no enlargement of the liver, peripheral edema or other evidence of failure of the right heart, but in whom the high tension in the pulmonary circuit is evidenced by dyspnea, accentuation of the pulmonic second sound, diminished vital capacity, etc. In such cases, hemoptysis is part of the symptomatology of left heart failure. I have seen several instances of mitral stenosis in which hemoptysis that recurred many times during the stage of isolated left heart failure ceased after the right heart had also given way. However, the hemoptysis of pulmonary engorgement may also continue or be intensified after the right ventricle has failed. In these cases, the blood may emanate from infarcts or the tension in the pulmonary circuit may continue high despite the insufficiency of the right ventricle, just as high systemic arterial pressure is often maintained by the severely insufficient left ventricle Proft[25] has suggested that the bronchial vessels, which drain into the systemic veins, may be the source of some of the hemoptyses accompanying right heart failure, but the significance of this factor remains to be demonstrated.

Another moment that may be of significance in the genesis of cardiac hemoptysis is disease of the pulmonary vessels. When hypertension of the lesser circulation has been present for some time, the pulmonary arteries are generally more or less atherosclerotic and the thickened capillary walls exhibit hyaline and other regressive changes. Connective tissue proliferation in the intima may practically obliterate the lumen. As pointed out by Parker and Weiss,[13] the arteriolar lesions of chronic passive congestion of the lungs may even go on, in rare vessels, to necrosis of the wall resembling that seen in the renal arterioles in the malignant phase of essential hypertension. It is plausible, though by no means proven, that these lesions predispose to extravasation in the presence of high blood pressure. Libman[14] believes that the rare hemoptyses occurring during bouts of rheumatic fever are not always indicative of heart failure and are sometimes manifestations of damage to the pulmonary vessels by the rheumatic infection, being similar in pathogenesis to the more common epistaxis and one result of the widespread damage to the blood vessels during active rheumatic infection. Libman has found that infarction is most often absent in these instances of hemoptyses during active rheumatic infection, and regards the nature of the process in the vessels which leads to the bleeding as entirely obscure. Hemoptysis may also occur in the rare cases of primary pulmonary endarteritis.

Physical Findings.—Inspection often reveals the objective evidences of hyperpnea and cyanosis that have been described in the chapters on these signs. Emphysematous distention of the thorax may be present in long-standing cases (page 427). If the patient be requested to take a deep breath and then exhale as completely as he can, the diminished respiratory excursion of the chest generally indicates the lessened vital capacity. The vocal fremitus usually is little altered; with severe engorgement it may be diminished over the bases. Marked dulness over the bases is generally the result of pleural effusion or other complication. However, in intense engorgement comparison of the note with that present after improvement sometimes shows that the resonance was impaired, particularly over the bases. Especially in elderly patients who are intensely dyspneic, there may be a tympanitic overnote, evidently indicative of distention of the lungs (page 427); this tympanitic quality is sometimes present only during paroxysms of dyspnea. Tidal percussion of the bases often reveals the diminished respiratory excursion that results from the rigidity of the lungs. On auscultation, no abnormality may be detected even though the roentgen examination shows that the lungs are severely engorged. When the engorgement is severe, the breath sounds at the bases are often feeble. But the most common auscultatory evidence of pulmonary engorgement is the presence of numerous

fine râles, either most numerous or more often exclusively in the lower lobes. While these basal râles are most often bilateral, they may be unilateral without the reason being obvious either from the other clinical findings or the roentgen picture. Following coronary occlusion, the râles are sometimes confined to the left base and may thus lead to an erroneous diagnosis of bronchopneumonia. Occasionally sibilant and sonorous râles are present throughout the chest, and their connection with the engorgement is demonstrated when they disappear as the heart improves; presumably, they result from the bronchial catarrh

ROENTGEN FINDINGS IN PULMONARY ENGORGEMENT

The x-ray appearance is usually characteristic and often of aid in detecting the presence and estimating the severity of pulmonary engorgement. However, there are also atypical pictures, and I *have several times known the roentgen film to occasion incorrect* diagnosis, notably of metastatic carcinoma, bronchopneumonia, miliary tuberculosis, or pneumokoniosis, despite the fact that clinical symptomatology pointed clearly to heart failure. The roentgen picture of pulmonary engorgement may include changes in the hilus shadows, the lung markings, the lung fields proper, and the pleura

1 **The Hilus Shadows.**—In pulmonary engorgement, with rare exceptions, the hilus shadows are more prominent than in health, being increased in both density and size. When the engorgement is extreme, the hilus shadows may be so large and dense that mediastinal or bronchial neoplasm is simulated While the enlargement of the hilus shadows is bilateral, it may be largely masked on the left side by the massive heart. With improvement of the heart, the density and size of the hilus shadows generally decrease. Assmann[1] has attempted to follow quasi-quantitatively the course of pulmonary engorgement by measuring the breadth of the shadow of the right pulmonary artery just after it turns downward to supply the middle and lower lobes of the lung He finds that in health the diameter in the teleoroentgenogram of this part of the pulmonary artery is between 11 and 14 mm., while in pulmonary engorgement it is between 15 and 23 mm , and even more in some instances of dilatation due to congenital heart disease. However, it is not always feasible to outline the borders of this vessel even in good films.

Marked expansile pulsation of the hilus shadows (not merely transmitted pulsation) is often, but by no means always present in pulmonary engorgement. It may be so striking that Pezzi[24] has called it the hilar dance. The pulsation is in the pulmonary arteries, which expand during cardiac systole. Whether such pulsation, when marked, is indicative of functional insufficiency of the pul-

monic valve, as maintained by Pezzi, remains to be determined In any event, it should be borne in mind that expansile pulsation of the hilus shadows is often discernible in thin-chested individuals without pulmonary engorgement. It is also seen in many cases of patent ductus Botalli and, according to Pezzi, in heart block with *very high pulse pressure. I have also seen it in heart block, here, it is due to the large stroke volume of the right ventricle*

Assmann attributes the lion's share of the enlargement and greater density of the hilus shadows in pulmonary engorgement to dilata-



FIG 1 —Pulmonary engorgement due to failure of the hypertensive and arteriosclerotic heart Increase in size and density of the hilus shadows and pulmonary markings

tion of the pulmonary artery, the structure which he has shown to contribute most of the hilus shadow in health In most instances, this is readily seen to be the case But in those instances in which the hilus shadows are so solid and dense as to simulate a tumor, it would seem that other structures must also contribute At postmortem, the pulmonary veins can often be seen to be so greatly distended that they must be of significance in the formation of the hilus shadow of pulmonary engorgement Further, in many instances of heart failure, especially when active rheumatic fever

is present, the tracheobronchial glands are so greatly enlarged that they probably form more than an insignificant part of the hilus shadow.

2. **The Lung Markings**.—The lung markings are also more prominent in pulmonary engorgement than in health, being both denser and thicker. The normal lung markings are known to be largely the shadows of the vessels, and their accentuation in pulmonary engorgement is largely a manifestation of the distention of the vessels. Zdansky[32] found that distention of the perivascular lymphatics also contributes to the accentuation of the lung markings in pulmonary engorgement, but this is probably a relatively insignificant factor. The engorgement of the vessels may be so great that those running a considerable course perpendicular to the film throw dense round shadows which may dot the film like those of carcinomatosis, miliary tuberculosis, or pneumonoconiosis, for all of which I have known them to be taken. Another factor that often contributes to the increased density of the markings of the chronically engorged lung is fibrosis. In long-standing pulmonary engorgement the foci of fibrosis and hemosiderosis always present anatomically may appear as minute nodular or strand-like opacities in the film. Exceptionally, the calcification of such foci is discernible (see Munk[13] and Gross and Mueller[8]) and should not be confused with healed tubercles. Sometimes, but not always, these nodule-like shadows diminish in number and density toward the periphery of each lung. Often, they are more numerous in the lower lobes and may then simulate bronchopneumonia.

3. **The Lung Fields**.—The lung fields proper between the lung markings appear denser, *i. e.*, more radio-opaque, in pulmonary engorgement. They have a cloudy appearance which sometimes makes one think that the film is technically imperfect. When the engorgement occurs in an emphysematous lung, the increased density may not be evident, being neutralized by the pulmonary rarefaction. Usually, the clouding of the lung fields is more pronounced in the lower lobes. It is often impossible to differentiate the increased density due to engorgement from that of pneumonic consolidation; of course, both not uncommonly co-exist. While shadows due to engorgement are usually rather symmetrical in the two lungs, this is not always the case. Zdansky found that localized areas of pulmonary edema due to engorgement may occasion areas of increased density in the film which simulate localized patches of bronchopneumonia; I have also often seen this. The increased density of the lung fields in pulmonary engorgement is due to the greater filling of the small vessels, the thickening of the interalveolar septa, and the presence of transudate in the alveoli.

4. **The Pleura**. Pulmonary engorgement may be accompanied by pleural effusion or edematous thickening of the pleura. Accord-

ing to Zdansky, the visceral pleura or pleural adhesions may swell as a result of edema in pulmonary engorgement so as to simulate the roentgen appearance of small pleural effusion

THE VITAL CAPACITY AND OTHER RESPIRATORY VOLUMES IN PULMONARY ENGORGEMENT

One of the most remarkable and clinically significant manifestations of pulmonary engorgement is the deleterious effect on the mechanics of ventilation and the air content of the lungs The study of the respiratory volumes has served to visualize, with perhaps greater clarity than any other method of investigation, the manner in which passive congestion of the lungs handicaps ventilation The important rôle of impaired ventilation in the pathogenesis of cardiac dyspnea has already been discussed (page 121). Here, we may briefly summarize the more important changes in the individual respiratory volumes that result from pulmonary engorgement:

1. The *total capacity* or total lung volume (the volume of air in the lungs at maximum inspiration) is *decreased* in pulmonary engorgement.
2. The *vital capacity* (the volume of air which can be expelled by maximum expiration following maximum inspiration) is likewise *decreased* in pulmonary engorgement, not only absolutely but also in relation to the total capacity
3. The *residual air* (the air remaining in the lungs after maximum expiration) may be either increased, decreased or unchanged in pulmonary engorgement, but always forms a *larger fraction of the total capacity* than in health (Binger[2]).
4. The *middle capacity* (the air content of the lungs midway between the inspiratory and expiratory positions) is *decreased* in pulmonary engorgement (Binger), but forms a larger fraction of the total capacity than in health (Rubow[23])
5. The *tidal air* (volume of the individual respirations) is *diminished* by pulmonary engorgement In very exceptional instances of heart failure, other mechanisms (page 134) cause an increase in the depth of breathing
6. The *minute volume of ventilation* is *increased* above the normal in pulmonary engorgement (page 126), augmentation in rate more than atoning for the diminution in tidal air.

The rationale of these changes in the respiratory volumes has been elucidated by Binger He points out that pulmonary engorgement affects the respiratory volumes in two ways: (1) The rigidity of the lungs is increased by engorgement of the vessels and, in longstanding cases, by brown induration (page 210); (2) as a result of protrusion of the distended capillaries into the alveolar spaces,

edema, and thickening of the septa, the actual volume of air space is diminished Both of these factors diminish the total capacity and the vital capacity, which are therefore always decreased in notable pulmonary engorgement. But in the case of the residual air, their effects are opposite and tend to neutralize one another. Greater rigidity of the lung prevents expiration from being as complete as normally, and thus tends to increase the volume of air remaining in the lungs after maximum expiration, *i. e.*, the residual air. On the other hand, the encroachment on the alveoli by the distended capillaries, edema and thickening of the septa tends to diminish the residual air. Depending, therefore, on which of these factors is in the ascendant, the residual air is increased or decreased. It is interesting that Binger found the residual air larger than normal in compensated heart disease; here it would seem, the higher pressure in the pulmonary vessels is the only factor operating. The finding that the middle capacity, though absolutely decreased, forms a larger percentage of the total capacity than in health, indicates that the chest is held in a more "inspiratory" position than normally Rubow offers a teleological interpretation of this relative increase in middle capacity. He holds that the severely dyspneic cardiac patient breathes so as to increase the relative middle capacity because the greater average distention of the lungs lessens the resistance to blood flow through the pulmonary circuit and thus tends to diminish the engorgement of the lung with its attendant dyspnea and orthopnea. However, this explanation seems improbable in view of the fact that the pulmonary engorgement is a consequence of weakness of the left heart and not due to augmentation of resistance in the lungs Binger believes that the greater relative middle capacity is a consequence of the increased pressure in the vessels of the engorged lungs, *i. e.*, that the tendency of the patient with cardiac dyspnea to breathe with his chest relatively more inflated is due to the rigidity of the lung, which opposes expiration.

Of the various respiratory volumes, the *vital capacity* is the one which has been used almost exclusively in clinical work. This is largely because of the ease with which it is estimated and because the only apparatus needed is a spirometer The patient is instructed to inhale as deeply as possible and then to exhale as completely as he can into the spirometer, the reading of which is the vital capacity. But in addition to the facility of determination, the vital capacity is a better index of heart failure than the total capacity, because it is depressed proportionately more by pulmonary engorgement.

The Vital Capacity in Health.—This varies with the size, sex and muscular development of the individual These factors must therefore be taken into consideration in formulating standards of nor-

mality. Hutchinson[12] originally used a height standard. Lundsgaard and Van Slyke[16] refer the vital capacity to the volume of the thorax, which they compute from its linear measurements. However, the most widely used standard is that of the surface area of the body. As might have been anticipated from the corresponding proportionality of the basal metabolism, Dreyer[5] and West[30] have shown that the vital capacity in health is closely proportional to the surface area of the body. The surface area is a function of the height and weight, and knowing the latter can immediately be obtained from the convenient chart of Du Bois and Du Bois According to West, the normal vital capacity in cubic centimeters is approximated by multiplying the surface area in square centimeters by the factor 2.5 in men, 2 in women, and 2 8 in athletes. In patients who are very edematous and whose previous weight is unknown, or who are very obese, it may be better to calculate normal vital capacity from the height alone West finds that the prediction of vital capacity from height alone is almost as accurate as from surface area, he estimates the normal vital capacity in cubic centimeters by multiplying the height in centimeters by the factor 25 in men, 20 in women, and 29 in athletes After the age of fifty, there is progressive diminution in vital capacity with advancing years In children, Edwards and Wilson[7] found an average vital capacity of 15 5 cc. for each centimeter of height According to Christie and Beams,[4] the vital capacity averages 5 5 per cent more in the upright than in the recumbent position

Interpretation of Decreased Vital Capacity.—With any of the above standards, decrease in vital capacity of less than 15 per cent below "normal" can scarcely be considered as pathological Indeed, one often obtains readings considerably lower than this which cannot be referred to any pathological cause Just as athletes have high vital capacity, many asthenic and sedentary individuals have low vital capacity, although this is by no means invariable Among city dwellers who have led sedentary lives, there are many who have never learned to draw a deep breath and who therefore simulate a low vital capacity It is a common observation that higher readings are obtained in successive attempts as the patient becomes more familiar with the maneuver.

In well-marked *heart failure* the vital capacity is reduced. In a general way, the reduction in vital capacity parallels the severity of left heart failure with its resultant pulmonary engorgement. In severe cardiac insufficiency the vital capacity may be less than 25 per cent of the normal, values of less than a liter in adults are not rarities. Peabody[22] found that cardiac patients with a vital capacity of between 70 and 90 per cent of the normal were generally dyspneic on moderate exertion, though most often capable of some work. Those with vital capacity of between 40 and 70 per cent of

normal were dyspneic on the slightest exertion and often confined to bed, while those with vital capacity of less than 40 per cent of normal were almost always bed-ridden Pratt[25] and others have shown that changes in the severity of cardiac insufficiency are generally accompanied by corresponding variations in vital capacity. Patients with well-compensated cardiac lesions have either a normal or but slightly decreased vital capacity. It is not always possible to rule out mild cardiac failure by the measurement of the vital capacity, there are individuals with cardiac lesions and dyspnea on moderate exertion in whom the vital capacity is not below the lower limit of normal.

The vital capacity is also decreased in many conditions other than heart failure Among these perhaps the most important are diseases of the lungs The vital capacity is almost always lowered in those pulmonary lesions which cause dyspnea or cyanosis and may thus be confused with heart disease (emphysema, interstitial fibrosis, extensive tuberculosis, lobar and bronchial pneumonia, neoplasms, etc). The same is true of pleural effusion, extensive pleural adhesions which produce symptoms, and pneumothorax. During attacks of bronchial asthma the vital capacity is of course much reduced, but between the paroxysms Myers[19] found the vital capacity within normal limits unless there was emphysema or another complicating lesion The vital capacity is generally *reduced in hyperthyroidism; indeed, Rabinowitch[27] found a roughly* inverse relationship between the vital capacity and the basal metabolism in Graves' disease. The decreased vital capacity in hyperthyroidism has been attributed to cardiac weakness (Lemon and Moersch,[13] McKinlay[16]), but it seems possible that the severe muscular asthenia of many of these patients also plays a part. The increased circulating blood volume in Graves' disease may result in a greater blood content of the lungs, with equal diminution in air content Muscular weakness *per se* often results in decrease in vital capacity, low readings are common in chronically ill patients without disease of the heart or lungs.

Because of these limitations, the clinical utility of the study of vital capacity is not great As already indicated, it adds little, if anything, to what is learned from the symptoms and physical signs. Dyspnea and other symptoms generally reveal heart failure before the vital capacity is significantly decreased. And in most of the conditions which may be confused with heart failure, the vital capacity may also be decreased The vital capacity is sometimes charted to follow the progress of a patient with heart failure, but adds little to the record of the symptoms and physical signs.

Harrison's ventilation index has already been discussed (page 129).

Other Respiratory Volumes.—Measurements of the *total capacity* and the *residual air* have been little used in clinical medicine for the

reasons mentioned above. The total capacity is calculated from the dilution of a known quantity of oxygen in a bag into which the patient breathes. (See Peters and Van Slyke[23] for technic.) The residual air is obtained by subtracting the vital capacity from the total capacity. The changes in the total capacity and residual air due to heart failure have already been mentioned (page 221). The respiratory volumes in emphysema are discussed on page 532

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CHAPTER XIV

THE LUNGS. II EDEMA, INFARCTION, AND BRONCHOPNEUMONIA

PULMONARY EDEMA

More or less transudation into the alveoli occurs in every instance of passive engorgement of the lungs. While practically always demonstrable histologically as coagulated albuminous fluid in at least scattered alveoli in the lower lobes, the edema is often not sufficiently extensive to produce clinical evidences. In other cases, the edema reveals itself solely by moist râles at the bases or by the presence of considerable amounts of protein in the sputum. An omnipresent danger in every patient with engorged lungs is that this minimal transudation will increase sufficiently to form the massive pulmonary edema that constitutes perhaps the most redoubtable and the most dramatic of the complications of pulmonary engorgement.

Occurrence.—It has just been mentioned that slight pulmonary edema is present in all instances of passive congestion of the lungs. But the frequency with which this minimal transudation rises to the dignity of massive pulmonary edema varies greatly in different forms of heart failure In a general way, massive pulmonary edema is most apt to develop in those conditions in which paroxysmal dyspnea (cardiac asthma) is most common Indeed, it is quite probable that more or less pulmonary edema occurs in most, if not all, severe attacks of paroxysmal dyspnea in cardiac failure.

In mitral stenosis with a small left ventricle, despite the frequency of pulmonary engorgement, massive pulmonary edema (other than terminal) rarely occurs, and even then usually only as a result of special exciting factors Episodes of pulmonary edema may follow unwonted physical exertion or sexual intercourse. Of interest is that fact that pregnancy predisposes to pulmonary edema in women with mitral stenosis (Sejourne[23]). I have seen repeated attacks of pulmonary edema during pregnancy in two women with mitral stenosis who did not have them before or after. They may occur at any time during pregnancy, but are probably more frequent during delivery. Acute left ventricular failure with pulmonary edema is a grave and not very rare development in the hypertensive toxemia of pregnancy (see Reid and Teel[20]), here, the tendency to water retention characteristic of toxemia presumably favors the occurrence of pulmonary edema when the left ventricle weakens. Bronchopneumonia in patients with mitral stenosis may be com-

plicated by massive pulmonary edema very early in the course of the inflammation; indeed, the existence of pneumonia in a cardiac patient who succumbs to pulmonary edema may first be evident at necropsy.

The true domain of massive pulmonary edema is insufficiency of the left ventricle. It is always a danger in the left ventricular failure of coronary artery disease, essential hypertension, acute and chronic glomerulonephritis, syphilitic and rheumatic aortic regurgitation, aortic stenosis, and those instances of mitral disease in which regurgitation predominates for a long time and the left ventricle is very large Pulmonary edema may appear very early in left ventricular failure; indeed, a severe or even fatal attack may usher in the clinical picture in an individual who had not previously considered himself sick. It is a condition that the ambulance physician not uncommonly encounters in the streets Pulmonary edema may develop with terrifying suddenness in patients with left ventricular strain even though there was little or no evidence of engorgement of the lesser circulation prior to the onset of the attack. Pulmonary edema may follow edema of the glottis in hypertensive individuals Those who survive one episode of pulmonary edema are predisposed to further attacks These may occur almost daily for a time, or there may be intervals of months or years (three years in a man with arteriosclerotic heart disease) Some patients have dozens of attacks. On the other hand, there are many patients with left ventricular failure and intensely engorged lungs who never develop pulmonary edema

Exceptionally, massive pulmonary edema is precipitated in an individual with left ventricular failure by physical exertion or some other coefficient which increases the work of the heart. Rare, but clear-cut, examples of such a sequence of events are seen in those cases of widely fluctuating hypertension in which pulmonary edema follows an extreme rise in blood pressure Thus, in a man with essential hypertension whose blood pressure was usually around 240/140 mm., on two occasions a few months apart, a rise in arterial tension to about 300/180 mm. was followed by pulmonary edema, he survived both attacks, later to succumb to uremia The hypertensive paroxysms of chromaffine tumor may be accompanied by pulmonary edema. Overenthusiastic examination of a patient with engorged lungs, including especially forceful abdominal palpation, is occasionally followed by pulmonary edema. Sometimes pulmonary edema is precipitated by copious intravenous infusions of salt or sugar solution. I have seen this especially in elderly individuals who were given intravenous infusions following operation That pulmonary edema may develop in cardiac patients in connection with pneumonia has already been mentioned; of course, this also occurs without pre-existent heart disease On very rare

occasions, massive pulmonary edema has been observed to follow the aspiration of large pleural effusions, but this also has not been confined to cardiac patients

Much more often, there is no obvious cause for the precipitation of pulmonary edema in left ventricular failure. Indeed, as is the case with paroxysmal dyspnea in general, bouts of pulmonary edema are especially apt to appear during sleep. The little that is known about the mechanism of this remarkable phenomenon is discussed in connection with cardiac asthma (Chapter VIII); there is good reason to believe that similar mechanisms operate to produce both cardiac asthma and pulmonary edema.

Massive pulmonary edema is a great rarity in the right ventricular failure of emphysema and other primary pulmonary diseases; when it occurs under such circumstances, it is presumably the result of some complicating affection of the left heart or is of inflammatory origin. Pulmonary edema is also very unusual when the heart fails in hyperthyroidism. Edema of the lungs in pneumonia is discussed in Chapter XXXII

Pathological Anatomy.—When massive pulmonary edema is present at the end, cyanosis is usually deep. The mouth, trachea and large bronchi often contain frothy fluid, which may even be seen in the nostrils The edematous lung does not collapse much when the chest is opened and crepitates little. It is large, heavy and soggy The depression produced by the palpating finger remains On section, the cut surface is moist and fluid drips or is readily expressed The fluid is either clear or pink from admixed blood; rarely, it has a dirty brownish color in lungs which are the seat of deep brown induration The fluid is generally, but not always, more or less frothy because of the presence of numerous fine air bubbles. According to Orth,[18] the presence of air bubbles proves the intravital origin of the edema, while in transudation which has occurred agonally or postmortem the fluid may contain no air However, in chronic edema the fluid is often devoid of air bubbles The color of the cut surface varies; sometimes, the red of engorgement dominates, but more often it is gray and pale

If the subject has succumbed to an acute episode of edema resulting from heart failure, the edema is usually universally distributed throughout both lungs On the other hand, chronic edema in heart disease is often confined to the lower lobes. Such areas of chronic edema may be rather gelatinous and the fluid expressed fairly thick from admixture of cells, resembling that scraped from a pneumonic infiltration; actually, chronically edematous lungs usually contain areas of bronchopneumonia. When the chronic edema implicates an atelectatic area, which is very common, the tissue presents the moist, dark red appearance of splenization. Localized inflammatory

edema collateral to foci of pneumonia is common in the lungs of those who succumb to heart failure

Pulmonary edema differs from edema in other parts of the body in that the fluid is not almost entirely in the interstices of the tissues, but much more in the alveolar lumens, which are really outside of the physiological interior of the body The reason for this peculiarity seems to lie in the morphological adaptation of the lung to its respiratory function The capillaries lie very close to the surface of the alveoli and are covered by only a thin layer of alveolar epithelium, which probably does not form a continuous covering. The result is that fluid which transudes from the capillaries immediately finds its way into the alveolar spaces. Because the fluid is rich in protein, it coagulates during the preparation of the sections, and is seen in hematoxylin-eosin preparations as pink-stained substance filling out the affected alveoli. Within it are vacuoles due to air bubbles The fluid contains varying numbers of blood and alveolar cells, but in non-inflammatory edema these are usually not numerous Where the alveoli are distended by the edema fluid, the interalveolar septa are compressed and the capillaries collapsed.

Pathogenesis.—The pathogenesis of pulmonary edema in heart failure has been the subject of controversy since the famous experiments of Welch.[25] This investigator was able to produce massive pulmonary edema in the rabbit by compressing the left ventricle He therefore attributed pulmonary edema in cardiac disease to weakness of the left ventricle: as a result of the disproportionately more powerful contraction of the right ventricle the lungs become engorged and the increased pressure in the pulmonary circuit results in transudation. This "mechanical" theory of Welch was disputed by Sahli.[22] He found that it is much more difficult in the dog than in the rabbit to produce pulmonary edema by compressing the aorta, left ventricle or pulmonary veins The output of the left ventricle must be so greatly decreased that convulsions or other evidences of cerebral ischemia appear before pulmonary edema develops. Since this sequence of events occurs but rarely in human pulmonary edema, Sahli believed that Welch's mechanical theory cannot account for most instances of pulmonary edema in human cardiac disease, and invoked an increase in the permeability of the pulmonary capillaries as the usual cause of the transudation.

Since the pioneer experiments of Welch and Sahli, numerous efforts have been made to elucidate the pathogenesis of pulmonary edema in heart disease on the basis of elevated capillary pressure or increase in the permeability of the capillaries. It would, however, seem that more than one pathogenetic factor may be concerned in the production of pulmonary edema in cardiac failure. This is rendered probable by consideration of the results of recent

investigations into the pathogenesis of systemic edema in cardiac and renal disease. These studies have shown that the formation of such peripheral edema *is a result of displacement of the equilibrium* between the hydrostatic pressure in the capillaries and the colloid osmotic pressure of the plasma in favor of the former, so that the volume of fluid that leaves the capillaries is greater than that which enters these vessels from the tissues. Such a displacement of the balance between hydrostatic and colloid osmotic pressure may result from: (1) Increase in the hydrostatic pressure in the capillaries; (2) decrease in the colloid osmotic pressure of the plasma; (3) increase in the permeability of the capillary wall to protein. We will consider the significance of each of these factors for the pathogenesis of pulmonary edema in heart disease.

1. Increase in Capillary Pressure in the Lungs.—The circumstances under which pulmonary edema develops in heart disease speak strongly for the primary significance of this factor. We have seen that pulmonary edema occurs almost exclusively in those forms of cardiac disease in which the left heart becomes insufficient with the result that the lungs become engorged and the blood pressure in the pulmonary circuit rises. Massive pulmonary edema is most to be feared in just those forms of heart disease in which attacks of cardiac asthma are common, *i. e.*, left ventricular failure as it occurs in nephritic and essential hypertension, coronary artery disease, and aortic valvular defects. Moreover, pulmonary edema may develop when the arterial pressure rises rapidly in patients with fluctuating hypertension, an observation which it is hard to explain on any other basis than acute insufficiency of the left heart with overloading of the pulmonary circuit. The same is true of those instances of coronary thrombosis with infarction of the left ventricle in which pulmonary edema rapidly proves fatal. Another phenomenon that speaks in the same sense is the often brilliant therapeutic efficacy of venesection in patients with pulmonary edema, improvement is often evident before the needle is withdrawn from the vein. That such venesection acts at least largely by diminishing engorgement of the lungs and consequently the pulmonary blood pressure would seem very probable, and is supported by roentgenograms before and after the blood letting, which often discloses a striking diminution in pulmonary engorgement after the removal of 500 or 700 cc. of blood. That pulmonary edema has been produced experimentally by obstructing the aorta or left ventricle was mentioned above. Subsequent studies by Loewitt[15] and others have shown that the reason that some investigators failed to bring about pulmonary edema by such procedures was that they failed to secure an adequate venous return to the right heart, a condition which is essential to the production of pulmonary engorgement and which is fulfilled in human left ventricular failure

In work with the heart-lung preparation, pulmonary edema develops if the resistance in the aorta is raised so high that the left ventricle gradually becomes insufficient.

In the light of these observations, there would seem to be little doubt that engorgement and consequent high pressure in the pulmonary circuit due to weakness of the left heart is the underlying cause of pulmonary edema in cardiac failure However, the important question still remains to be answered why paroxysms of massive pulmonary edema are so much more common in the left ventricular failure of hypertension, coronary sclerosis and aortic valvular disease than in mitral stenosis with its chronic pulmonary engorgement and long-standing, low-grade edema of the lower lobes. The answer to this question is not clear, but may be connected with the suddenness with which pulmonary engorgement develops. When the left ventricle fails, there may be sudden overloading of the pulmonary circuit On the other hand, in mitral stenosis the engorgement of the pulmonary bed usually develops gradually. Indeed, when there is sudden overloading of the pulmonary circuit in mitral stenosis as a result of violent exertion, edema of the lungs may quickly develop and prove fatal

Parenthetically, it may be mentioned that Cohnheim[3] attributed to left ventricular failure the pulmonary edema that is so common a terminal manifestation in many diseases He stated that it had been known since Haller's observations that when the heart dies the left ventricle stops contracting before the right He believed that this results in pulmonary engorgement and consequently edema In other words, as Cohnheim put it, the patient does not die because he has pulmonary edema but gets pulmonary edema because he is dying.

2. **Decrease in the Colloid Osmotic Pressure of the Plasma** —This is the mechanism of nephrotic edema and also often plays an accessory rôle in the peripheral edema of right heart failure. It may well be that pulmonary edema occurs more readily when the colloid osmotic pressure of the plasma is diminished. But the plasma proteins are normal in many patients with pulmonary edema (as I have found on a number of occasions) and therefore diminution in the colloid osmotic pressure of the plasma cannot be a necessary condition for the development of pulmonary edema. Indeed, in patients with chronic nephrosis or the nephrotic type of glomerulonephritis and very low plasma protein concentration, massive peripheral edema may be present for months or years and yet pulmonary edema does not develop unless as a complication of bronchopneumonia. I am unable to explain why, in such cases, edema does not appear in the lungs as it does in the subcutaneous tissues and serous cavities. The reason may be connected with

relatively low hydrostatic pressure in the very wide pulmonary capillaries, but this is purely hypothetical

3 **Increase in the Permeability of the Capillaries to Protein.**—This is the primary cause of edema in acute glomerulonephritis and in inflamed areas, and plays an accessory rôle in producing the peripheral edema of right heart failure. The mechanism by which increased permeability of the capillaries to protein leads to edema is probably that the plasma protein which passes into the tissue spaces there exerts a colloid osmotic pressure and thus tends to retain fluid in the tissues Since the fluid of pulmonary edema has a high-protein content—2 or 3 per cent or even more—it is evident that the permeability of the capillaries in the lung is actually increased Such increase in capillary permeability must facilitate the formation of edema How pulmonary engorgement increases the permeability of the capillaries remains to be elucidated Landis[13] found that when capillaries are deprived of oxygen for three minutes their permeability to protein is increased, and it may be that slowing of blood flow through an engorged lung has a similar effect Further, Krogh[14] has adduced experimental evidence that dilatation of a capillary increases its permeability to protein, inasmuch as the capillaries of the engorged lung are greatly distended, this mechanism may also participate.

The foregoing discussion has been confined entirely to the pathogenesis of edema of the lung in heart failure However, the same factors doubtless participate in the causation of other forms of pulmonary edema. Farber[4] finds that aberrations in the dynamics of the pulmonary circulation due to disturbances in vasomotor control are concerned in the causation of the pulmonary edema that follows bilateral cervical vagotomy, and the same is presumably true of the edema of the lung that may complicate cerebral vascular accidents in man Increased capillary permeability appears to have been the primary cause of the massive pulmonary edema that was so often fatal in gas poisoning during the first World War. Edema of the lungs in pneumonia is discussed on page 666.

Clinical Picture.—It has already been mentioned that at least minimal degrees of pulmonary edema are practically always present in pulmonary engorgement. While even slight transudation into the alveoli presumably plays some part in the genesis of such symptoms of pulmonary engorgement as dyspnea and cyanosis, there is no means by which the clinician can recognize it with certainty. The presence of crepitant râles at the bases in pulmonary engorgement is often taken as indicative of edema. However, such râles are often due merely to marginal atelectasis, which is common in even healthy elderly persons, and is especially frequent in pulmonary engorgement where the rigidity of the lung interferes with complete

expansion. Even the fact that such râles persist after a number of deep breaths does not of itself speak against their atelectatic origin. But when the basal râles in an engorged lung are subcrepitant and moist, transudation into the alveoli is indicated. The presence of considerable amounts of protein in the sputum is also evidence of edema.

On the other hand, massive pulmonary edema generally produces a dramatic clinical picture and characteristic physical signs The onset is usually sudden It may follow one of the above-mentioned exciting factors, but more often the attack appears out of a clear sky; indeed, the most common time of onset is at night, during sleep The patient experiences a sense of suffocation and thoracic oppression. Often there is a feeling of constriction about the neck. The difficulty in catching his breath forces the patient to sit up gasping There may be a tickling in the throat which is sometimes the first symptom. There are a number of short, rapidly repeated coughs. At first, these are usually unproductive, but soon the patient begins to bring up pink-stained or colorless, frothy, thin sputum. In milder attacks, there may be only a little of this sputum brought up in a few coughs and the paroxysm is over. Often, the injection of morphine aborts the attack at this stage. But in more severe seizures he continues to cough up larger volumes, and in fulminating paroxysms the edema fluid is brought up in mouthfuls and may even flow from the nose. The dyspnea is agonizing, the patient sits bending forward and coughing up mouthfuls of fluid between gasps, the cyanosis of the lips and finger tips deepens, the skin is pale and covered with cold sweat, the hands and feet are cold, and the expression of the face and eyes testifies to the fear of death which the patient afterward describes if he survives

When the sufferer is seen at the height of an attack of massive pulmonary edema, the sight of the copious expectoration generally establishes the diagnosis at a glance. On further inspection, the distention of the chest is usually evident, and percussion reveals the downward displacement of the lower borders of the lung The percussion note is hyperresonant or even tympanitic. But the characteristic physical findings are those on auscultation, in fact, the râles and tracheal rattling may be audible at a distance. In the very first stages, râles may not be audible and the only abnormality heard is harsh, loud breath sounds But soon the râles appear, starting at the bases and spreading upward to fill the lungs with bubbling adventitious sounds of all sizes. Generally, the râles are so loud and numerous that the character of the breath sounds cannot be made out and the heart sounds are inaudible.

While the arterial pressure often falls, especially in cases of coronary thrombosis, *in my experience a rise has been much more common.* I have seen a rise of over 70 mm under these circumstances.

The elevation of arterial pressure during pulmonary edema may sometimes be due to asphyctic stimulation of the vasomotor center. However, the rise in pressure is often pronounced before the signs of edema are manifest, and when cyanosis is still absent. Here, it may be difficult to distinguish between cause and effect. The rise in pressure may be the cause of the left ventricular failure and pulmonary edema; or, on the other hand, the rise in pressure may be due to vasoconstriction reflexly called forth by the diminution of cardiac output due to the failure of the left ventricle.

During a major attack of pulmonary edema, the venous pressure generally rises because the violent expiratory efforts and cough raise the intrapleural pressure and thus interfere with the return of blood from the peripheral veins. However, on a number of occasions when the patient could lie still for a sufficient time following the injection of morphine, I have found the venous pressure within normal limits. Indeed, in a recent instance of pulmonary edema in coronary thrombosis, the venous pressure was less than 2 cm. of water Sometimes, the liver enlarges acutely during an attack of pulmonary edema, but this is exceptional.

The roentgen picture reveals a clouding of the lung fields Sometimes, this clouding appears almost uniform, but usually it can be seen to be due to the confluence of individual cloudy areas.

The volume of edema fluid expectorated varies. There are severe and even fatal attacks of pulmonary edema in which little or no fluid is actually expectorated. On the other hand, in some attacks as much as a pint is brought up in an hour or two, and total quantities of over a liter have been recorded. The edema fluid is characterized by its large content of protein, which may amount to 2 or 3 per cent. The fluid usually contains red blood cells in varying number; when abundant, the fluid is pink.

The attack may terminate in recovery or death at any time. Sometimes, it is over in a minute or two, while in other cases it lasts for hours or even a day or two. The rapidity with which the patient may recover, either spontaneously or as a result of treatment, is often remarkable. After a nocturnal attack he may drop off to sleep, with or without the aid of morphine, and awake the next morning feeling as usual. One hypertensive individual, who had had many major attacks of pulmonary edema, always nocturnal, did not even bother to call a doctor after the first few. It is often surprising how quickly the râles disappear from the chest after recovery from a bout of pulmonary edema

A fatal outcome may ensue at any stage of the attack. Pulmonary edema is one of the causes of sudden death in heart disease, the victim being found dead in bed or on the street with the characteristic pink, frothy fluid on his lips. In other instances, the attack terminates fatally only after hours or even days In the last stages,

the cough and expectoration often cease ("bronchoplegic stage"); as already mentioned, in rapidly fatal cases, no fluid may be brought up. Occasionally, convulsions usher in the end, presumably, they are due to cerebral anoxemia. However, I once saw recovery from an attack of pulmonary edema with unconsciousness and several epileptiform convulsions.

In addition to the fulminant, acute form of pulmonary edema just described, there are also instances of *chronic pulmonary edema* They usually come on insidiously, I have not seen them start with a fulminant attack. Chronic pulmonary edema usually involves only the lower parts of the lungs but may be more widespread It may last for days or weeks. The symptoms are those of severe engorgement of the lungs and the physical signs consist in moist bubbling râles of all sizes and usually dulness on percussion, the latter may be as marked as in pneumonic consolidation and then may be indicative of combination of edema with atelectasis (splenization). The roentgen film reveals clouding of the edematous parts There may be little or no cough and expectoration, but in other cases the patient brings up abundant sputum which is rich in protein and may be bloody.

It should be mentioned that copious pulmonary edema is not uncommonly found at necropsy despite the fact that examination a short time before death revealed none of the characteristic râles, presumably, it originated agonally

HEMORRHAGIC INFARCTION OF THE LUNG

Hemorrhagic infarction of the lung is a common complication of pulmonary engorgement. The incidence at necropsy is much higher than at the bedside, for infarcts often cause no characteristic symptoms or signs Kugel and Lichtman[12] found pulmonary infarcts in 35 per cent of 424 necropsies on individuals with heart disease Most frequent in long-standing pulmonary engorgement and patients who have been bed-ridden because of heart failure, infarction also occurs exceptionally in individuals who are up and about, and very rarely is even an initial manifestation of heart disease. Not very rarely, seemingly smooth recovery from a bout of heart failure is abruptly halted and reversed by the development of an infarct in the lungs, this is sometimes so striking that it has been attributed, without adequate proof, to liberation of mural thrombi from the right heart as a result of more forceful contraction of the recuperating or digitalized heart muscle. Infarction has seemed to me decidedly more common in elderly patients It may complicate pulmonary engorgement of any origin, much the largest contingents being supplied by those with mitral defects and those with hypertensive and arteriosclerotic heart disease. The statis-

tics of Levine and White[14] show that pulmonary infarction complicates a much higher proportion of instances of heart failure in mitral stenosis than in hypertension. Many instances of so-called bronchopneumonia in patients with chronic pulmonary engorgement are in reality primarily infarcts. And on several occasions necropsy has revealed the same to be true in aged individuals who were not known to have heart disease and were considered clinically to suffer from pneumonia

The following description will be restricted to hemorrhagic infarction as observed in the pulmonary engorgement of heart failure. Pulmonary embolism without infarction is described in Chapter XXVIII

Pathological Anatomy.—Hemorrhagic infarction of the lung in heart failure may be single, especially when very large, but more often there are multiple and occasionally numerous infarcts. They are most commonly situated in the lower and middle lobes. The right lung is more often affected, apparently because the right pulmonary artery is wider and is a more direct continuation of the stem, so that emboli are more apt to enter it. Almost always subpleural, and very rare in the vicinity of the hilus, infarcts involve with especial frequency the sharp margins of the lower and middle lobes including those of the interlobar fissures Infarcts most often vary in size between that of a grape and of a plum, but occasionally there is massive infarction of the larger part of a lobe. Because of their subpleural location, infarcts are generally discernible before the lung is sectioned. They appear as rounded or polyhedral, dark red, bluish or almost black, slightly elevated, quite definitely delimited areas which are firm or hard to the touch. Over them, the pleura has generally lost its luster and may be covered with obvious fibrinous exudate On section of the lung, the infarct is generally found to be wedge-shaped, the base on the pleura and the apex pointing to the hilus; it is dark red or almost black, but turns red on exposure to the air Older infarcts are brownish in color. The cut surface is firm or hard, often granular like in pneumonia, and in most instances little is scraped off by the knife, although in fresh infarcts some thick bloody fluid sometimes containing minute black granules of clotted blood may be thus obtained. The lesion is devoid of air and does not crepitate. Careful dissection almost always discloses a plugged artery at the apex of the infarct. The plug is adherent, of varying size and stage of organization; upstream to it is often a propagated clot. The accompanying veins are generally also thrombosed

Microscopically, the most striking feature is the inundation of the alveoli with blood; the air spaces are packed tight with erythrocytes, admixed with which are scattered leukocytes and alveolar epithelia. Some of the latter contain hemosiderin; such heart

failure cells are very abundant in many older infarcts. The Weigert stain often reveals an irregular network of fibrin In very fresh infarcts there may be comparatively little change in the structure of the interalveolar septa However, the characteristic finding is that of coagulation necrosis, the nuclei staining either defectively or not at all. Hyaline thrombosis of the capillaries is commonly present. At the periphery of the infarct, there is usually leukocytic reaction which may be marked enough to form a blue staining wall like that seen so well around infarcts of the kidney In older infarcts, the formation of granulation tissue at the periphery has already begun.

Hemorrhagic infarction often results in bloody or clear pleural effusion.

The picture of fresh or relatively recent infarction, just described, is the one most commonly encountered at necropsy However, hemorrhagic infarcts may also undergo secondary regressive changes or healing.

The secondary changes are softening with sequestration and cavity formation (aputrid necrosis), infection with gangrene or abscess formation, and transformation into a blood cyst, all are very rare. I saw a patient with mitral stenosis who, under observation, developed three cavities in the lungs which seemed to be the result of breaking down of infarcts, but unfortunately there was no necropsy to confirm the clinical and roentgenographic diagnosis. As a result of these secondary changes and rupture into the pleura, pneumothorax and empyema may occur, but are great rarities

If the patient does not succumb too soon, which is most often the case, infarcts undergo healing through organization and fibroid transformation. The blood pigment is altered so that the lesion becomes rusty brown or yellow in color; on rare occasions depigmentation of hemorrhagic infarcts has been observed (Karsner and Ash[8]). Granulation tissue grows from the periphery inward and the resultant connective tissue finally becomes condensed into a scar. The overlying visceral pleura becomes thickened and the contraction of the connective tissue may result in a puckered depression; or else a pleural adhesion forms The clots in the artery and vein supplying the involved area become organized. It is not rare to find infarcts of various ages in the same lung; and careful search *would probably reveal the inconspicuous scars of old infarcts* to be more common in the lungs of cardiac patients than is generally realized.

Pathogenesis.—Extensive experimental, anatomical and clinical investigations have shown that two primary factors supplement one another in the pathogenesis of hemorrhagic infarction of the lungs

1 Occlusion of a medium-sized branch of the pulmonary artery.
2. Passive engorgement of the lungs.

Arterial Occlusion.—Complete embolization of the main stem of the pulmonary artery is so quickly fatal that there is no time for infarction. While embolic occlusion of the right or left pulmonary artery is often survived, and may indeed be asymptomatic and a surprise at necropsy, infarction likewise does not result This is probably largely because the individuals who survive embolization of the right or left main pulmonary branch have sound hearts and therefore do not fulfil the other condition necessary for the development of infarction, namely, pulmonary engorgement. At the other end of the scale, occlusion of very small branches of the pulmonary artery also does not lead to infarction, the collateral circulation from the branches of the bronchial artery and the anastomoses of the remarkable wide capillaries sufficing for the nutrition of the involved parenchyma. It is after occlusion of medium-sized branches of the pulmonary artery that infarction occurs. Such occlusion can be demonstrated almost invariably in the form of an adherent clot in the branch of the pulmonary artery that enters the apex of the wedge-shaped pulmonary infarct That the plugging of the artery is the cause of the infarct, and not *vice versa*, is immediately evident from the pyramidal shape of the infarct, corresponding to the distribution of the occluded artery. Moreover, the artery distal to the occlusion may be entirely patent in the midst of the infarcted tissue

There has been considerable discussion regarding the nature of the arterial occlusion, whether it is embolic or thrombotic. In many comparatively fresh cases, the structure of the plug and comparison of it with the type of clot in the right heart or systemic veins leaves no doubt that it is embolic; indeed, characteristic riding emboli at an arterial bifurcation are not rare. For these reasons, it is generally thought that in the vast majority of instances hemorrhagic infarction is of embolic origin. However, this is by no means always actually demonstrable, and does not mean that some of the hemorrhagic infarctions complicating pulmonary engorgement may not be due to primary thrombosis of the occluded vessel. Well-marked atherosclerosis of the pulmonary arteries is the rule in protracted engorgement of the lungs due to mitral stenosis and other forms of left heart failure, and in combination with the slowing of blood flow may well be the basis on which thrombosis develops. The frequency of thrombosis of the pulmonary arteries in engorged lungs is in need of further study.

The source of the emboli, whether from the right heart or from the systemic veins, is often obscure clinically and sometimes at necropsy. In many cases, the emboli demonstrably emanate from the right heart, notably the appendage of the dilated right auricle, as well as from mural thrombosis of the right auricle proper or the right ventricle In other instances, pulmonary emboli originate

in thrombi in the systemic veins, notably in the pelvis and lower extremities The latter are a much more common source of emboli than is generally appreciated because dissection of the veins of the lower extremities is most often omitted at the necropsy of cardiac patients and edema that may have been present during life can be readily explained on the basis of heart failure. On a number of occasions, I have seen extensive thrombosis of the veins of the lower extremities in individuals succumbing to heart failure despite the fact that there were no definite signs or symptoms of the clotting during life. Doubtless, the retardation of the venous flow in right heart failure and the bed-ridden state of the cardiac patient both predispose to venous thrombosis, especially in the lower extremities. On a number of occasions, I have first found the evidences of a venous thrombosis in the lower extremities after pulmonary embolism occurred The great frequency of systemic venous thrombosis in right heart failure is indicated by the careful study of Belt[1] He found that of 83 such patients, 36 had thrombi in the venous side of the circulation, the veins of the lower extremities or pelvis being the site in 20 Belt points out that the greater the local reaction about a venous thrombus, the less the likelihood that a large embolus will break off

Passive Engorgement of the Lungs —Though there is no doubt that arterial occlusion is the primary cause of hemorrhagic infarction in heart failure, the blocking of the artery does not *per se* suffice to bring about the infarction. Postmortem observation reveals that in individuals with unimpaired circulation, a bland* pulmonary embolus generally does not result in infarction, indeed, Lubarsch[17] found at necropsy that only 29 per cent of pulmonary emboli produced infarcts. Furthermore, it has repeatedly been demonstrated in animal experiments that bland embolization of the pulmonary arterial branches does not result in infarction when the general circulation is not impaired. Thus Karsner and Ash[8] found that when they embolized the pulmonary artery with seeds, while the territory of the occluded branches exhibited such changes as congestion, edema, swelling and desquamation of the epithelium, and conglutination of red corpuscles, true infarction with necrosis did not result But when the embolization was combined with passive congestion, produced either by ligating the vein of the lobe or compressing it with fluid in the pleural cavity, a true infarct resulted. Similar experiments with the same results have been conducted by others Human postmortem experience is the same, plugging of a branch of the pulmonary artery results in infarction only when the general circulation through the lung is impaired.

* Infected pulmonary emboli, on the contrary, often produce infarction in the absence of slowing of blood flow, here the factor of capillary damage by the infection is probably important

The way in which passive congestion of the lungs promotes hemorrhagic infarction of the territory supplied by an occluded branch of the pulmonary artery is probably as follows: When the general circulation through the lungs is rapid, occlusion of an artery results in the minor circulatory disturbances mentioned in the preceding paragraph, but not in true infarction because the collateral circulation supplied from the bronchial arteries and the remarkably wide pulmonary capillaries (the widest in the body, see page 207) suffices to prevent necrosis. But when the lung is the seat of passive congestion with its retardation of blood flow, the collateral circulation thus supplied is too slow to make up for the loss of the arterial supply However, it is largely the presence of these collateral sources of blood, insufficient though they are to maintain the vitality of the tissues, that makes the infarction of the lung a hemorrhagic one That venous backflow is not the sole cause of the hemorrhagic nature of the infarct is shown by the finding that experimental infarction of the lung is hemorrhagic even if the vein of the area is ligated at the same time as the artery.

It was mentioned above that hyaline thrombi in the capillaries of the infarcted area as well as thrombosis of the efferent veins are often, though by no means always, present. However, there is every reason to believe that these are secondary lesions and not originally responsible for the infarction.

Anemic infarcts of the lung are great rarities. According to Kauffmann,[9] they may follow arterial occlusion in old and decrepit persons, in whom the circulation is slow although there is no engorgement

Clinical Picture.—Very often, infarction of the lung occasions no characteristic symptoms. Occurring in a patient already having the symptoms and physical signs of pulmonary engorgement, and perhaps also of bronchopneumonia, those due to superadded infarction may not be differentiable It is very common to find at the necropsy of such a patient multiple infarcts of various sizes and ages, the existence of which had not been suspected, or at least not definitely demonstrable, during life. The aggravation of heart failure often occurs *pari passu* with the development of extensive pulmonary infarction; here, it may be difficult to differentiate cause and effect. It is readily conceivable that pulmonary arterial occlusion and infarction, through augmenting the work of the right ventricle and intensifying anoxemia, may aggravate heart failure.

In other cardiac patients, pulmonary infarction produces characteristic clinical pictures.

The onset may be sudden and dramatic. The symptoms are those of the actual embolization and like, although usually less severe than, those of emboli lodging in the trunk or main branches of the pulmonary artery (page 553). The patient complains of

sudden thoracic oppression and dyspnea, he becomes very anxious and sits up gasping for breath, the lips and finger tips are livid, the skin pale, cold and clammy, the pulse is rapid and often hardly palpable; in short, the picture is that of shock I have several times known such cases to be confused with coronary thrombosis and once with pneumothorax Later, the blood spitting and other evidences of the actual infarction appear and the case is clear. However, death from shock may supervene as a result of such embolization of a medium-sized branch of the pulmonary artery before there is time for the actual infarct to develop

Much more often, the first symptoms are those of the actual infarction, without clear-cut manifestations of the embolization *per se* There is a sticking pain in the side, usually intensified by deep breathing, cough appears, dyspnea and cyanosis are aggravated, physical examination may reveal circumscribed dulness and a shower of râles with or without a pleural friction rub at the painful area, and some hours later thick, bloody sputum is coughed up. This is the classical onset, but there are many variations

Chill.—Not rarely, the first symptom of pulmonary infarction is a chill or chilly sensation. This may precede the pain in the side by several hours, and is perhaps to be attributed to the actual embolization.

Thoracic Pain.—Thoracic pain is a common, but by no means a constant symptom. It is unilateral, and most often in the axilla or under the angle of the scapula Usually, the pain is pleuritic in character, causing the patient to splint the affected side and accentuated by deep breathing. A dull, constant ache is also encountered. The pain is often accompanied by tenderness of the overlying chest wall When the diaphragmatic surface is involved, the pain may be referred to the abdomen or shoulder, such cases have been mistaken for acute abdominal ailments With diaphragmatic involvement, the patient may complain of pain in the shoulder when upward pressure is exerted on the corresponding upper quadrant of the abdomen. The pain of pulmonary infarction usually passes away in a day or two, but may last with varying severity for weeks.

Cough and Hemoptysis.—Cough usually appears sooner or later, and may be an initial manifestation At first it is often short, paroxysmal and unproductive, being frequently doubtless of pleuritic origin. The rule is that the characteristic bloody *sputum* is not brought up until about six to twenty-four hours after the initial pain, but sometimes it is the first symptom. The sputum is often uniformly dark red in color and so tenacious that it sticks to the patient's lips and to the sides of the sputum box In other cases, streaks or clots of blood are expectorated in an otherwise mucoid sputum. After a few days, the blood in the sputum usually becomes

darker red or even black and finally turns brown as the blood pigment in the infarct is altered. However, the expectoration of red, *bloody sputum may continue for weeks. In exceptional cases,* as has already been mentioned, infarcts result in copious *hemoptysis,* which may be repeated. In one patient with infarction of an entire lobe, the repeated copious hemoptyses reduced the hemoglobin to about 25 per cent The appearance of large numbers of heart failure cells in the sputum of hemorrhagic infarction has likewise been noted above There are also many instances of hemorrhagic infarction in which bloody sputum is not present. I have repeatedly seen multiple hemorrhagic infarcts of the lung at the necropsy of patients who did not have sanguineous expectoration; apparently, either clotting of the blood within the alveoli or some other obstacle prevented the extravasated blood from reaching the bronchi.

Dyspnea and Cyanosis.—Dyspnea and cyanosis are usually aggravated by pulmonary infarction and may become very intense. In previously well-compensated patients, these symptoms may be initiated by infarction Several factors are probably concerned. For one thing, the pleuritic pain often renders respiration superficial so that the ventilation of the lungs is inadequate and breathing rapid. And while the portion of the total pulmonary arterial cross-section obstructed is usually comparatively small, the increment in resistance may be significant because of the pre-existent hypertension of the lesser circulation On several occasions, I have observed that pulmonary infarction was quickly followed by swelling of the liver and superficial veins (in one patient the venous pressure rose 11 cm. within twenty-four hours), indicating that the right heart had failed to meet the additional burden thrust upon it by the occlusion Further, the decrease in breathing surface due to the infarction may not be insignificant because of the handicaps to respiration already present as a result of the pulmonary engorgement. All of these factors become more significant when there are multiple infarcts of the lungs; then, the cyanosis and dyspnea are usually pronounced.

Fever —Fever may or may not be present in pulmonary infarction Even large infarcts are sometimes unaccompanied by fever at the start, a circumstance that facilitates the often difficult differential diagnosis from pneumonia. Most often, there is low-grade fever, but not uncommonly the temperature reaches 102° or 103° F. The fever usually disappears within a few days but may last for two weeks or longer Presumably, the fever is analogous in pathogenesis to that of myocardial infarction and is part of the reaction to the necrosis of pulmonary tissue and extravasation of blood. Of course, the possibility of secondary pneumonia must always be borne in mind when the pyrexia persists However, the diagnosis of complicating pneumonia in a pulmonary infarction merely because the fever continues for a week or two is not justified Occasionally,

fever first appears when pleural effusion complicates the infarction. The fever of pulmonary infarctión is generally accompanied by moderate polymorphonuclear *leukocytosis.*

Jaundice.—Low-grade jaundice, usually limited to a subicteric tint of the scleræ, is not uncommon in patients with pulmonary infarction A rare event is the sudden development of frank jaundice following pulmonary infarction, it was observed by Libman[15] and I[5] have seen it only twice although I have taken especial pains to look for it since a study of the subject seventeen years ago In both cases, it appeared about two days after massive infarction and the first patient narrowly escaped operation for gall-bladder disease. The relation of pulmonary infarcts to jaundice is further discussed on page 259.

Physical Signs.—The physical signs of hemorrhagic infarction vary, and are often obscured by the concomitant presence of signs due to the general engorgement of the lungs or edema There are many instances of infarction which cannot be localized from the physical signs although their existence is revealed by the symptoms and sputum. The signs of an infarct are most often detected over the bases posteriorly or in the lower axilla, and less commonly in other parts of the chest Usually, the first findings are localized showers of moist râles Or pleural friction may be the first definite sign of an infarction which is already evident from the symptoms. The only abnormality on auscultation apart from the râles and perhaps the friction may be feeble breathing, but more often the breath sounds are broncho-vesicular and accompanied by somewhat bronchial whispered voice. If the infarct is large, dulness appears; most often, it is but moderate, although exceptionally the note is almost flat and leads to confusion with effusion It is obvious that the physical signs in themselves do not suffice to differentiate infarction from pneumonic consolidation.

Roentgen Picture.—The roentgen picture of pulmonary infarction is not as characteristic, in the vast majority of instances, as might be expected. Usually, the patient with a large infarct is too sick to have other than a bedside film And often the shadow due to infarction is obscured by the general engorgement of the lower lobes. The most common roentgen expression of pulmonary infarction is uneven and poorly outlined clouding indistinguishable in itself from pneumonic consolidation *Occasionally, rather sharply delimited* shadows are produced by infarcts. But only exceptionally are they sufficiently characteristic to be differentiated from the shadows of consolidation without knowledge of the clinical picture Most distinctive, though unusual, is a triangular shadow based laterally which is produced when a large, wedge-shaped infarct is situated with its long axis perpendicular to the roentgen-rays. On rare occasions necrosis in an infarct results in one or more cavities (I once

saw three in a patient with mitral stenosis), and the healing of an infarct with scar-production may be revealed by a linear shadow (see Smith[24])

Electrocardiographic changes resulting from pulmonary embolization are described on page 556.

Pleural Effusion.—Pleural effusion is a common complication of hemorrhagic infarction It may be clear but more often is bloody. The effusion usually first becomes evident several days after the infarction and may recur after tapping. Occasionally, bloody effusions in cardiac patients develop as a result of infarction which has not itself been clinically evident.

Other *rare complications* of pulmonary infarction in heart failure are pulmonary abscess or gangrene, empyema and pneumothorax. Actually, these complications are so rare as a result of bland emboli that when they occur one should always search for a septic focus from which infected emboli may have originated. Pericarditis was observed by Werner[26] to complicate pulmonary infarction in 3 cases; he attributed it to propagation from the pleurisy over the infarct. I have also recently noted a pericardial rub of about a day's duration in a patient with pulmonary infarction

Prognosis.—The prognosis of pulmonary infarction is always serious In a general way, infarction is a phenomenon of the last stages of heart disease. Often the appearance of pulmonary infarcts marks the transition in long-standing heart disease from the stage of good or tolerable compensation to a period of steady decline and progressively increasing cardiac insufficiency. However, some patients survive a number of infarcts and are later able to be up and about. A girl with mitral stenosis who was able to do light work had had an infarct seven years previously and another later. The chief immediate danger in pulmonary infarction is the development of bronchopneumonia. I have not known hemoptysis from infarction to prove directly fatal. Cardiac patients who have survived infarction are especially liable to have subsequent infarcts

BRONCHOPNEUMONIA

Bronchopneumonia is a common and redoubtable complication of pulmonary engorgement It is especially frequent during the winter and spring months in patients who have been bed-ridden for a considerable time as a result of heart failure. Probably the most common termination of chronic cardiac disease is with bronchopneumonia, although very often the pulmonary infection merely adds the *coup de grâce* where death is close as a more direct consequence of circulatory failure

There are probably various reasons for the frequency of bronchopneumonia in pulmonary engorgement. The congestion and conse-

quent swelling of the bronchial mucous membrane probably interfere with the efficiency of the mechanism which normally removes particulate matter, including bacteria, that enter the bronchi with the inspired air. Areas of atelectasis, infarction, extravasation and edema offer a favorable soil for the survival and proliferation of bacteria which reach them Actually, many cases of so-called bronchopneumonia in cardiac patients are primarily infarcts with secondary inflammatory reaction In individuals with pulmonary engorgement, upper respiratory infection is much more apt to be followed by bronchopneumonia than in otherwise healthy persons

A question that has aroused much investigation and controversy is that of the nature of the pneumonic foci that so often occur in severe bouts of rheumatic fever. They are rarely absent when active rheumatic fever proves fatal. Thus, Gouley and Eiman[7] observed acute inflammation of the lung with consolidation in 8 of 9 individuals succumbing to active rheumatic fever, and the other had subacute pulmonary inflammation with pleurisy. Klinge[10] describes the histological picture as that of an "uncharacteristic" inflammation with hemorrhages, marked edema, swelling of the intercellular substance of the connective tissue, and abundant proliferation of large connective tissue cells, the latter of which he regards as similar to what is found in the heart valves Paul[19] has also emphasized the extremely hemorrhagic character of the intra-alveolar exudate In one of Coburn's[2] cases he remarks that the polymorphonuclear leukocytes are subordinated to the lymphocytes and large mononuclear cells Paul found widespread panarteritis of the pulmonary arterioles in from 20 to 40 per cent of the active cases While Klinge and Paul observed Aschoff bodies in the wall and adventitia of the pulmonary artery, the former investigator did not find them in the pulmonary tissue proper Most other investigators have likewise failed to find Aschoff bodies in the pneumonic consolidations of rheumatic fever, and this has also been the experience of Drs Louis Gross and Paul Klemperer in the large material at Mount Sinai Hospital On the other hand, Fraser[6] claims to have demonstrated lesions of the nature of the Aschoff body in two instances of virulent and rapidly fatal rheumatic fever And Goulet and Eiman describe pulmonary lesions "identical in morphology with those found in rheumatic heart lesions " Pleurisy is almost always present

Despite the fact that it is still questionable whether the inflammatory reaction in the lung leads to the formation of granulomata analogous to the Aschoff bodies of the heart, to the writer there would seem little room for doubt that many of the pulmonary lesions appearing during active rheumatic fever are true "rheumatic pneumonia," *i e*, part and parcel of the rheumatic infection, just as are the lesions in the heart and joints Especially in children with rheumatic fever, one sees the development of pneumonia in conjunction with pancarditis and arthritis so often that it is hard to avoid the inference that the pulmonary, the cardiac and the articular lesions are parallel manifestations resulting from a common pathogenetic process In two recent cases of rheumatic pneumonia, I have found evidence that the lesions did not result from pulmonary engorgement due to heart failure, for the pulmonary circulation time was normal.

Bronchopneumonia complicating pulmonary engorgement may run various courses. Often, it is first discovered at necropsy, having caused neither symptoms nor signs which could be differen-

tiated from those of the antecedent passive congestion of the lungs. The fever may be low grade or even almost absent despite extensive consolidation Dyspnea, cyanosis and other manifestations of heart failure are usually intensified. Peculiarly enough, this is quite often not true of peripheral edema due to right heart failure, which may diminish during bronchopneumonia while the other evidences of cardiac weakness become more pronounced. This paradoxical behavior is perhaps to be attributed, at least partially, to the increase in insensible perspiration due to the fever. On the other hand, it is not rare for bronchopneumonia in engorged lungs to be complicated by pulmonary edema, a very grave complication which has been called serous pneumonia because of the inflammatory nature of the edema fluid The clinical course of bronchopneumonia complicating pulmonary engorgement is often very protracted and trying; low-grade fever may persist for even a month or more. Frequently, râles and other physical signs persist long after the fever has disappeared

Needless to say, the prognosis must always be guarded when pneumonia develops in a patient with cardiac insufficiency. The mortality is high, more so when the pulmonary engorgement is due to arteriosclerotic heart disease in older persons than when it results from rheumatic heart disease. Nevertheless, many cardiac patients survive a number of attacks of severe bronchopneumonia. Some children with rheumatic heart disease have one or more attacks of pneumonia every year, usually during the spring or winter, for several years. However, probably a majority of these pneumonias are not complications of pulmonary engorgement, for they may occur in the absence of circulatory failure and are then often part and parcel of the rheumatic fever

The pulmonary complications of coronary thrombosis are discussed on page 455 and those of peripheral circulatory failure on page 621

PULMONARY ENGORGEMENT AND TUBERCULOSIS

While bronchopneumonia so readily develops in engorged lungs, they are rarely the seat of active tuberculosis. This fact was pointed out by Rokitansky,[21] who stated that those diseases of the heart and arteries which are manifested by cardiac enlargement, cyanosis and dropsy are not accompanied by phthisis. Subsequent observations have confirmed that active pulmonary tuberculosis is rare in mitral stenosis, coronary artery disease and other conditions leading to passive congestion of the lungs. Dr. Maurice Fishberg told me that in the Tuberculosis Service of Montefiore Hospital (350 beds) during a period of ten years there were only about half a dozen cases of active and progressive pulmonary

tuberculosis in patients with evidence of pulmonary engorgement from mitral stenosis. However, it is not rare to note on the roentgen film or at the postmortem table the scars of healed tuberculous lesions in lungs which are the seat of chronic engorgement from valvular or arteriosclerotic heart disease, these are doubtless legacies from infections which occurred before the engorgement of the lungs In good accord with the conception that engorgement of the lungs creates a poor soil for the development of tuberculosis is the well-known fact that a large percentage of those with congenital pulmonary stenosis who reach adolescence succumb to pulmonary tuberculosis

An interesting clinical fact, that may be mentioned in passing, is that when a patient with fibroid phthisis develops arterial hypertension, copious and repeated hemoptysis is apt to dominate the clinical picture; I have seen several such cases, two of which succumbed to exsanguination. The hemoptysis apparently does not always result from pulmonary engorgement due to heart failure, for there may be neither symptoms nor roentgen evidence of such engorgement.

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CHAPTER XV

THE LIVER AND SPLEEN

THE LIVER

SWELLING of the liver is one of the common manifestations of heart failure Indeed, there are cases of cardiac insufficiency—the *asystole hépatique* of the French—in which enlargement of the liver and recurrent ascites so dominate the clinical picture that careful study is needed to differentiate them from primary hepatic disease, and even then errors occur. The importance of hepatic engorgement for the dynamics of the circulation in heart failure will be clear when it is recalled that an engorged liver may contain more than 1500 cc. of blood, or about one-quarter of even the increased circulating blood volume of such patients

By far the most common cause of passive engorgement of the liver is *failure of the right heart.* There is every reason to regard this hepatic congestion as a direct mechanical consequence of the engorgement of the inferior vena cava The mechanical nature of the engorgement is evinced in long-standing cases by the pronounced dilatation and occasional atherosclerotic thickening of the hepatic veins (page 250) The hepatic veins empty into the inferior vena cava so close to the right auricle that one would anticipate that the liver would be immediately involved in the passive engorgement resulting from right heart failure. I have often seen palpable enlargement of the liver in right heart failure of so slight a degree that the pressure in the antecubital veins was within the normal range. In such cases, evidently, the liver participates in the repletion of the veins that precedes a rise in the pressure within them (page 109). Moreover, the very swelling of the liver may militate against elevation of venous pressure. Enlargement of the liver may be demonstrable within a few minutes after the onset of an attack of paroxysmal tachycardia with heart failure. On the other hand, when the heart is improving, enlargement of the liver may persist despite the fact that the pressure in the antecubital veins has returned to normal.

In addition to right heart failure, passive engorgement of the liver may occur as a result of the hypodiastolic heart failure of mediastino-pericarditis, pericardial effusion, and paroxysmal tachycardia (Chapter XXXI). Enlargement of the liver is not a feature of isolated left heart failure. In the peripheral circulatory failure (shock) induced in the dog by histamine and other agents, the liver becomes intensely engorged as a result of constriction of the

hepatic veins and dilatation of the hepatic capillaries (page 66). Whether there are forms of human shock with similar engorgement of the liver remains to be established

There is some evidence (Zak[13] and page 67) that in addition to the distention of the blood vessels, storage of water within the liver cells may play an accessory rôle in the tumefaction of the passively engorged liver Wenckebach[12] believes that it is the liberation of this stored fluid which accounts for the remarkably rapid shrinkage of the liver that sometimes occurs within a few hours after the administration of organic mercurial diuretics to cardiacs; however, improvement of the heart may also be concerned in this early detumescence of the liver

This chapter will be confined to a description of passive engorgement of the liver as it occurs in right heart failure, swelling of the liver in other forms of circulatory failure mentioned above will be considered in the respective sections

Pathological Anatomy of Engorgement of the Liver.—At postmortem, the engorged liver is generally found larger and heavier than normal, often weighing above 2500 grams However, in instances in which the liver has been engorged constantly or intermittently for years, the organ may be distinctly atrophic and weigh 1000 grams or less Comparison of the size of the liver at necropsy with that estimated during life usually reveals shrinkage as a result of escape of blood, which may become more marked after the organ is sectioned and the blood flows from the vessels. In an acutely engorged liver, wrinkling of the capsule may testify to the postmortem shrinkage

In fresh or relatively recent engorgement, the liver is dark red or purple, sometimes almost black, and the surface smooth The superficial veins are often prominent. When the engorgement is of long duration, the color becomes a dark, cyanotic brown with dots and streaks of yellow The surface may then be irregular in consequence of numerous irregular linear or flat depressions, such a liver is often of a tough or even hard consistency. The capsule may be thickened, especially if there was long-standing ascites The lower border is sometimes blunted

On section, the acinar structure of the freshly engorged liver is preternaturally distinct. This is due to the deep purple or red color of the center of each lobule caused by the engorgement of the central vein and neighboring capillaries, often combined with atrophy of the cords of liver cells between the latter. When the engorgement has been present more than a short time, the liver cells in the periphery of the lobule are yellow in color because of their fat content The result is the very characteristic appearance long ago termed "nutmeg liver" by Kiernan [14] The center of each lobule is red or purple while the confluent peripheries of the abutting

lobules are yellow. Owing to the atrophy of the liver cells, the red areas at the centers of the lobules are usually depressed below the level of the confluent yellow peripheries. When the engorgement is more severe or of longer duration, the central red areas of engorgement reach the periphery of the lobule to join with similar red areas from adjacent lobules (*Stauungsstrassen* of the Germans), so that the initial abnormally clear definition of the lobules becomes confused. Indeed, a false lobulation may appear, the center of each simulated lobule being formed by a yellow area composed of the confluent peripheries of several true lobules and bordered by the red areas of engorgement, the configuration is that of the Sabourin lobule, which has the portal space for its center. In advanced cases, the transformations often become so complicated that little can be made out with the naked eye of the architecture of the liver. Foci composed of dilated capillaries with only scattered small liver cells between them may coalesce so as to produce irregularly distributed areas of atrophy, red and depressed below the general level of the section. The picture is further complicated in some long-standing cases by the appearance of light yellow dots and streaks of regenerating liver cells, rarely, these merge to produce large, light, irregularly distributed areas, somewhat reminiscent of medullary cancer. Apparently, however, these light areas are not always due to regeneration, for Lambert and Allison[16] found that they may be merely the expression of less engorgement than in other parts of the liver. Sometimes, a few hemorrhages are present. Engorgement may be of varying intensity in different lobes of the liver. If jaundice is present, it is of course seen in the liver.

The hepatic veins are dilated. In long-standing cases, they may exhibit well-marked phlebosclerosis (Moschcowitz[25]).

Microscopic Findings.—The first changes consist in engorgement with dilatation of the central vein and the adjacent capillaries of the central part of the lobule. Soon the liver cells between the engorged capillaries are affected. They become atrophied and many appear as thin elements flattened between the distended capillaries. There may be extensive deposition of fat and brown pigment in these cells. The degenerative atrophy progresses so that many of the cells in the center of the lobule disappear entirely. The result is that the central part of the lobule may be transformed into a red area consisting almost entirely of the engorged central vein and capillaries, the original liver tissue being represented only by occasional atrophic cells. In the periphery of the lobule, fatty change in the liver cells is usually prominent from a relatively early stage. It is the contrast between the yellow periphery and the purplish-red center of the lobule that produces the nutmeg appearance in the gross. With advance of the process, as described above, the zone of distended capillaries with atrophy of the liver

cells may reach the periphery of the lobule and coalesce with similar areas of the adjacent lobules.

Another process which is significant in many, if not most, instances of severe passive engorgement is the focal hemorrhagic necrosis on which Mallory[23] laid so much emphasis. The liver cells in the center of the affected lobules, sometimes in other parts, become necrotic, so that their nuclei do not stain. In some instances the necrosis is so extensive as to involve whole lobules or groups of lobules. Usually, some of the areas of necrosis are also the seat of hemorrhage. The necrosis of course leads to the complete disintegration of the affected parenchyma, but when seen in an early stage the outlines of the liver cell cords may yet be preserved and the necrosis is revealed only by the fact that the nuclei do not take the hematoxylin.

The above are the most typical histological pictures, but many variants occur. Thus, there are cases (Lambert and Allison[16]) in which fatty change renders the center of the lobule yellow while there is a surrounding red ring as a result of hyperemia and perhaps necrosis of the mid-zone ("ring necrosis") Compression of the capillaries by edema fluid between the liver cell cords and capillaries has been described In long-standing cases, the picture becomes complicated by the changes in the reticular and collagenous skeleton to be described below, and sometimes by regeneration of liver cells in the periphery of the lobules. Bile thrombi have been found in the bile ducts by Eppinger,[7] but they are not numerous and not always demonstrable. For a detailed description and classification of the various histological pictures, the reader is referred to the paper of Lambert and Allison.[16]

Early observers referred the atrophy and other regressive changes in the liver cells to mechanical compression by the engorged and distended capillaries. Recently, the significance of this factor has been depreciated on the ground that the atrophy is initiated in the center of the lobule, while, since the flow is centripetal, the pressure must be higher in the periphery of the lobule However, this objection does not seem entirely valid From *intra vitam* study of the capillaries of the nail fold, it is known that in right heart failure the venous end of the capillaries is much more dilated than the arterial segment. That this is also the case in the liver seems very probable, and is indeed indicated by the frequent observation that in early engorgement only the capillaries in the central part of the lobule are distended Evidently, the pressure in the venous end of the capillary is relatively more elevated in right heart failure than is the pressure in the arterial end of the capillary, with resultant diminution in the pressure gradient along the capillary and slowing of blood flow. It is true that the pressure in the arterial end is still higher, else blood flow would be reversed, but elevation

above the normal is greater in the venous end, so that this part of the capillary is more distended and compresses the liver cells. The flattening of many of the liver cells could hardly be explained by other than mechanical compression. However, as pointed out by MacCallum[20] and others, mechanical pressure by distended capillaries is by no means the only agent damaging the liver cells in passive engorgement The topography of the lesions shows that other factors must also enter Quite probably, slowing of blood flow retards the metabolic exchanges between blood and liver cells and thus plays an important part in producing the fatty changes, cloudy swelling, atrophy, pigmentation, etc. Mallory[23] thought that the necroses are always of toxic origin and due to complicating infections. However, their very frequency renders this view improbable, and Bolton[4] and Zimmermann and Hillsman[34] have produced identical necroses by experimental obstruction of the inferior vena cava.

Cardiac Cirrhosis.—Since the time of Becquerel,[1] who first maintained the connection, the question has been debated whether cirrhosis of the liver is ever an outcome of long-standing passive congestion of the organ due to heart failure. The term cardiac cirrhosis was applied (see Cornil and Ranvier[6] for the older literature) to instances of hepatic cirrhosis thought to be the result of heart failure We have already mentioned that in long-standing passive engorgement of the liver, the organ may become reduced in size and weight, very firm, of a dark, cyanotic brown color, the capsule thickened, and the surface irregular as a result of numerous grooves and flat depressions produced by the atrophic and necrotic changes. Minute elevations due to islands of regenerated liver cells may also be present. Very rarely, the surface is even somewhat granular or nodular, though it seems questionable whether the granulation is ever as marked or regular as in classical portal cirrhosis.

In these long-standing cases of passive congestion of the liver, there is actually hyperplasia of the connective tissue framework. Herxheimer[10] showed that the reticulum fibers of the liver are hypertrophic and hyperplastic in protracted engorgement of the organ. And in some cases the central zone of the lobules is largely replaced by connective tissue This is not merely a condensation of pre-existent connective tissue due to atrophy and necrosis of the liver cells; active proliferation of fibroblasts may be evident. Very rarely, this central fibrosis extends to the periphery of the lobule so that strands of connective tissue connect adjacent lobules and even encapsulate islands of intact liver cells While hepatic fibrosis due to passive engorgement is characteristically and almost always initiated in the central zone of the lobule the observations of Katzin, Waller and Blumgart[12] indicate that, much less often, heart failure favors the development of periportal fibrosis.

The development of fibrosis in the passively congested liver has been attributed to complicating infections However, the experiments of Zimmermann and Hillsman[34] show that it may result purely from engorgement, for they found well-marked connective tissue proliferation about the central veins in protracted experimental obstruction of the inferior vena cava. Excellent evidence that prolonged right heart failure leads to fibrosis of the liver is also contained in the above-mentioned investigation of Katzin, Waller and Blumgart.[12] They found that in 286 cases in which death was due to heart failure, the incidence of hepatic fibrosis was three times as great as in 1714 control necropsies. The incidence and severity of the fibrosis of the liver increased with the duration of the right heart failure. Moreover, while fibrosis initiated in the central zone of the lobule is the most common form in heart failure, Katzin and his associates also found that periportal fibrosis was more common in patients succumbing to cardiac insufficiency than in controls Especially significant is their finding that central fibrosis, so common in the cardiacs, did not occur at all in the controls Boland and and Willius[3] have also recently published examples of "true cirrhosis" due to heart failure.

In the light of these findings, there would seem to be no room for doubt that protracted right heart failure leads to hepatic fibrosis On rare occasions—the rarity is worthy of reiteration—this intrahepatic fibrosis becomes sufficiently pronounced to impede the portal circulation and thus contribute to the production of ascites and splenomegaly In these exceptional cases, the use of the term cardiac cirrhosis seems warranted

Clinical Picture of Engorgement of the Liver.—Pain —Very often passive congestion occasions no subjective symptoms and is detected only by physical examination But in other instances, the swelling of the liver is accompanied by pain Indeed, there are rare instances of heart disease in which the first symptom is hepatic pain The pain is especially apt to occur when the engorgement of the liver sets in acutely, for instance in the sudden right heart failure that often accompanies the onset of auricular fibrillation In these cases, the pain may be of such sudden onset and severity that cholelithiasis or some other acute surgical condition is suspected, such patients have been subjected to operation The pain is usually localized in the right upper quadrant but may be epigastric. Especially when of sudden development, it may radiate to the back, the spine of the right scapula or the right shoulder, as in gall-stone colic. Usually, it is described as a soreness, heaviness, or dull ache which is intensified by movement or deep breathing and prevents the wearing of tight clothing; not rarely, the patient with an engorged liver splints his breathing like in pleurisy to prevent the squeezing of the liver by the increased intra-abdominal pressure during

inspiration There are also cases in which the pain is lancinating or colicky, one such patient with an arteriosclerotic heart, who also had icterus, was saved from laparotomy while being prepared for operation It is to be emphasized that there may be severe pain of hepatic origin when the enlargement of the liver is but slight, the lower edge reaching only 2 or 3 cm. below the costal margin. It is in such cases, in which the rigidity due to the tenderness and perhaps also gaseous distention interfere with palpation, that diagnostic difficulties are most apt to occur. On rare occasions, the hepatalgia of acute passive engorgement is accompanied by vomiting, presumably, this is actually a reflex manifestation of the swelling of the liver and analogous to the vomiting of gall-stone colic, but there is also the possibility that simultaneous engorgement of the stomach is also concerned.

The pain is usually most marked in the first days of the congestion and then diminishes But it may persist for months in less intense form. Most often the chronically engorged liver is painless or almost so, although increment in the swelling due to intensification of the heart failure may be evinced by exacerbation of the pain. It is often striking how rapidly intense liver pain vanishes when heart failure is mastered by digitalis or other measures.

The pain of hepatic engorgement is generally thought to be due to stretching of the capsule, which accounts for the fact that it is most apt to be severe in sudden congestion. Episodes of hepatic pain in long-standing engorgement, especially when intensified by deep breathing, are often attributed to perihepatitis. But I have never heard a friction rub in such a case, and the intensification by deep inspiration may well be a consequence of increased intra-abdominal pressure

Dyspeptic Symptoms.—Various dyspeptic symptoms often accompany the hepatic engorgement of heart failure Among them are anorexia, meteorism, eructations, constipation, occasional bouts of diarrhea, nausea, and rarely vomiting At the bedside of chronic bed-ridden cardiacs, these are among the most common complaints. But to what extent they are correlated with the engorgement of the liver, or with that of the gastro-intestinal tract or pancreas, is not clear

Enlargement.—Of the objective symptoms of passive engorgement of the liver, enlargement is the most constant. This varies from a size in which the lower edge is just palpable to an enormous tumor extending well below the umbilicus. Most of the extension of the engorged liver is downward. However, sometimes upward extension is revealed by elevation of the diaphragm with compression of the right lower lobe, which results in dulness and feeble breathing; this may be differentiated from the corresponding signs of pleural effusion by the relative mobility of the lower border of

the lung, unless pain limits the respiratory excursion. Usually, the enlargement is symmetrical, but when engorgement affects a liver which is ptosed or has a Riedel lobe or other deformity, peculiarly shaped tumors occasionally result which may lead to diagnostic difficulties. In long-standing engorgement with fibrosis, the liver may be very hard with either a sharp or somewhat blunted edge. The irregularities in cardiac fibrosis are not palpable. In rare, protracted cases, the fibrosis and other processes described in the section on pathological anatomy may cause shrinkage of the liver to above the costal margin

Tenderness.—The pain is accompanied by tenderness on palpation; indeed, very often the tenderness is present when the patient does not complain of spontaneous pain The tenderness may be associated with muscular rigidity and thus prevent accurate delimitation of the size of the liver Mackenzie[22] pointed out that the tenderness often extends well beyond the borders of the liver and may reach the right paravertebral region posteriorly For this reason, he concluded that the seat of the tenderness is in the skin and more especially the muscles. However, one can often convince oneself that the liver itself is also tender, for when the patient breathes while the hand is appropriately placed on the abdomen, tenderness may be elicited only when the edge strikes against the hand. In long-standing engorgement, the tenderness and muscular rigidity generally disappears

Pulsation.—The engorged liver may pulsate. It is necessary to differentiate true expansile pulsation from movements communicated to the liver by the heart, from which it is separated only by the diaphragm, or from the abdominal aorta Especially in instances of right ventricular enlargement, but also in the ample excursions of aortic incompetence, the movements communicated to the liver by the heart or aorta may simulate hepatic pulsation Sometimes differentiation by clinical means is very difficult, but most often careful palpation will enable one to determine whether the liver is actually expanding in volume with each heart beat or is merely being displaced It should be remembered that communicated movements of the liver are far more common than true pulsation. The so-called arterial pulsation of the liver in aortic insufficiency is probably most often, if not always, merely a transmitted movement.

There are two forms of liver pulse, the ventricular and the auricular. Each accompanies the corresponding type of venous pulse in the neck.

In the *ventricular form* of liver pulse, the organ is distended during ventricular systole just as are the cervical veins in the ventricular form of venous pulse. Usually, though not invariably, it occurs in the presence of auricular fibrillation. Since considerable

force is required to distend the liver, it is generally thought that the ventricular form of liver pulse indicates the existence of tricuspid insufficiency, either organic or more often relative. However, it is possible that the same mechanism which has been described on page 117 as causing the ventricular form of venous pulse may rarely produce a similar form of liver pulse merely as a result of great venous stasis and absent auricular systole, despite the absence of notable tricuspid incompetence

In the *auricular form* of liver pulse, the organ swells during auricular systole, *i e*, early ventricular diastole. Mackenzie[21] originally considered this form of liver pulse, of which frank examples are very rare, as pathognomonic of the right auricular hypertrophy of tricuspid stenosis But he later observed examples in the absence of tricuspid obstruction. Nevertheless, at least in the absence of other evidences of severe failure of the right heart, an auricular liver pulse is probably good evidence of tricuspid stenosis and is always very suggestive of this rare lesion As already mentioned, the auricular form of liver pulse accompanies a large auricular wave in the neck veins

Hepato-jugular Reflux.—An interesting phenomenon, long ago pointed out by William Pasteur,[28] is that when the engorged liver of the recumbent patient is manually compressed, the veins in the neck can be seen and felt to swell (hepato-jugular reflux of the French) The same swelling of the jugular veins can also be occasioned in patients with severe right heart failure by compression of other parts of the abdomen, for instance, the left lower quadrant. On the other hand, compression of an enlarged liver (*e g.*, a carcinomatous or cirrhotic organ) or another part of the abdomen in a patient with intact circulation does not cause swelling of the jugular veins, provided the patient is instructed to breathe as usual during the maneuver By measuring the pressure in the antecubital vein, my associate, Dr William M Hitzig, has found that while compression of the liver or lower abdomen in a subject with right heart failure causes a considerable rise in pressure (even 10 cm. of water), this is slight or absent in subjects with unimpaired circulation I have repeatedly found observation of the cervical veins during hepatic compression of aid in the differential diagnosis of enlargement of the liver The swelling of the cervical veins during hepatic compression is simply a sign of right heart failure When the right heart is insufficient, the right auricle does not empty as completely as in health The result is that the blood forced into the inferior vena cava and then into the right auricle by the abdominal compression is added to the residual blood in the right auricle and thus raises the intra-auricular pressure. In addition, as pointed out by Lian and Blondel,[17] the abdominal compression elevates the diaphragm and thus increases intrathoracic

pressure. These two factors result in greater resistance to the return from the superior vena cava and jugular veins, so that the blood flow within them is slowed and they swell. The swelling is all the more prominent because these veins were well filled previously in consequence of the right heart failure.

Tests of Hepatic Function—From the anatomical findings, it is obvious that the functional capacity of the liver must be diminished to some extent in severe engorgement. However, the factor of safety of the liver is so great that fatal hepatic insufficiency (cholemia) *apparently does not occur as a result of uncomplicated heart failure.** The hyperbilirubinemia that is the rule, and the jaundice that occasionally occurs, in severe heart failure are primarily due to impaired hepatic function (page 259). The liver damage is also evidenced by the fact that most patients with hepatic engorgement exhibit an increase in the urobilinogen content of the urine. According to Heilmeyer (page 270), the increased total pigment content of the urine in right heart failure is principally due to impaired liver function. The augmented lactic acid content of the blood that may occur in severe right heart failure is doubtless also at least partially the result of hepatic damage. Using the bromsulphalein test of liver function, Jolliffe[11] obtained evidence of impaired function in the form of retention of between 5 and 20 per cent of the dye in 12 of 16 patients with right heart failure. Bromsulphalein retention exceeding 5 per cent occurred in 14 of Cantarow's[5] 42 patients with heart failure of varying severity, in 2 there was 100 per cent retention. On the other hand, Jolliffe obtained a positive levulose tolerance test in but 3 of the 16 patients just mentioned. The disturbances in hepatic function due to heart failure do not seem to be documented in the cholesterol content of the blood, this was normal in Cantarow's cases, and I have several times observed a normal percentage of cholesterol esters in severe failure. As a result of a detailed study with various tests of liver function, Jolliffe found evidence of some impairment of liver function in 15 of 16 patients with right heart failure.

CARDIAC JAUNDICE

Increase in the bilirubin content of the blood is very common in severe *and protracted heart failure. It was present*[9] in 21 of 23 such patients in the Montefiore Hospital for Chronic Diseases, where most of the patients have been ill for over a year. On the other hand, hyperbilirubinemia was found in only 2 of 7 patients with severe heart failure of recent inception. These findings refer

* French clinicians (Villaret and Justin-Besançon[31]) have described a clinical picture akin to that of acute yellow atrophy with fatal cholemia in heart failure, but I have not seen this and would be inclined to view such liver damage as due to some complication

to patients with both right and left heart failure, and consequently both hepatic and pulmonary engorgement, a combination which seems to offer the optimum condition for icterus of cardiac origin In several patients with isolated left heart failure and intense engorgement of the lungs, the bilirubin content of the blood was not notably increased. Usually, the Van den Bergh reaction in the serum of patients with heart failure is delayed or indirect, but in exceptional instances with marked hyperbilirubinemia it is prompt and direct.

The hyperbilirubinemia of heart failure is not uncommonly accompanied by yellowish discoloration of the scleræ, which is not sufficiently deep to be recognized unequivocally as icteric. In exceptional instances, this is heightened to frank jaundice, which was present in 2.1 per cent of Jolliffe's 231 patients with heart failure, in 4 per cent of the 424 cases studied by Kugel and Lichtman,[15] and in 2 of the 42 reported by Cantarow. The icterus is especially apt to appear suddenly two to four days after pulmonary infarction I have never observed the jaundice of heart failure to be very deep, only on very rare occasions does the concentration of bilirubin in the serum exceed 5 mg. per cent. The combination of icteric scleræ and face with cyanotic lips and nose imparts a very characteristic appearance to the patient, so-called cyanotic icterus. Meakins[24] has pointed out that cyanotic icterus is usually visible only in those parts of the body which are free of edema. Similarly, Page[27] observed two patients with heart failure and hemiplegia who were edematous on the hemiplegic side; jaundice could be seen only on the other, nonedematous side. Searching for the explanation of this phenomenon, Meakins found that the edema fluid is almost devoid of bile pigment, which he attributes to the inability of the large bilirubin molecule to traverse the capillary wall. This explanation is doubted by Ottenberg,[illegible] who points out that bilirubin readily diffuses through membranes. He believes the low concentration of bilirubin in edema fluid to be a result of the low solubility of bilirubin, which is held in the blood adsorbed to protein, because of the low protein content of the edema fluid, little bilirubin can be held there.

Bilirubin appears in the urine in some instances of cardiac jaundice but more often it is absent. The amount of urobilinogen in the urine is increased (page [illegible]). The stools are not decolorized, indeed, they are usually dark and, according to Eppinger,[8] have a high content of bile pigment [illegible] lessens or vanishes

With improvement of [illegible] and the bilirubin content [illegible] The jaundice may reappear in some [illegible] compensation, or after pulmonary infarction [illegible] is a serious manifestation and most [illegible] succumb within a [illegible] short time.

Pathogenesis.—It is not entirely clear how heart failure produces hyperbilirubinemia and jaundice. However, available evidence indicates that three main mechanisms participate: (1) Impairment of liver function, (2) increase in the production of bilirubin; (3) diminution in blood flow through the liver

1. **Impairment of Liver Function.**—The very fact that the bilirubin content of the blood is elevated indicates that the ability of the liver to excrete the pigment is impaired. For the factor of safety of the healthy liver is so great—well over three-fourths of the organ can be ablated without jaundice resulting—that it is doubtful if the amount of bilirubin produced is ever so great as to result in icterus when the liver is functionally unimpaired (See Rich[29] for a splendid discussion of the general problem) The anatomical findings in chronic passive congestion of the liver have already been described. When severe and widespread, as is often the case, they seem adequate to explain the accumulation of bilirubin in the blood. But hyperbilirubinemia also occurs in instances of heart failure in which the sections reveal only atrophy of the central zone of the lobule and fatty deposition in the other parts In such cases, the damage to liver function must be an expression, not only of the lesions that can be seen under the microscope, but also of injury to the other liver cells which is not manifested by morphological changes demonstrable by present methods Rich, Resnik,[30] Keefer,[13] and their associates have brought forward strong evidence that the depression in the excretory function of the liver in heart failure is largely a result of oxygen deficiency They have shown that the same anatomical picture of central atrophy and fatty change in the liver is present in various circumstances in which the oxygen supply to the liver is deficient. This is true, for instance, in pernicious anemia, of which hyperbilirubinemia is a characteristic manifestation. And by repeated bleeding of animals, as well as by keeping them in a chamber with low-oxygen tension, they were able to produce lesions of the liver essentially the same as those present in chronic passive congestion, and to show that oxygen deficiency depresses the excretory function of the liver

The deficient oxygen supply to the liver cells in heart failure seems to be due not only to the slowing of blood flow through the liver, but even more to arterial anoxemia resulting from pulmonary lesions. Eppinger,[9] Libman,[18] Rich, and Keefer and Resnik have pointed out that the jaundice of heart failure is especially apt to develop in the wake of pulmonary infarction. The latter investigators believe that pulmonary infarction brings out jaundice largely through the intermediary of arterial anoxemia, for Binger, Brow and Branch[2] showed experimentally that multiple infarction of the lungs depresses the oxygen saturation of the arterial blood. Of course, a single infarction, even though massive, could have a

significant effect on the oxygenation of the blood only when the vital capacity is already diminished by engorgement, which is always the case in the patients now under consideration. That pulmonary infarction does not bring about cardiac jaundice through local formation of bilirubin from the extravasated blood has been demonstrated by Rich and Resnik. They injected volumes of blood comparable to those in large pulmonary infarcts into the muscles of patients with heart failure, but observed no increase in the bilirubin content of the blood. It is to be emphasized that pulmonary infarction, while present in most patients with cardiac jaundice, is not a *sine qua non* for the production of such icterus. Elevation of the bilirubin content of the blood is common in heart failure even though there is no pulmonary infarction, and I have also seen frank jaundice in the absence of infarcts of the lung.

All in all, it would appear that Rich and his associates have adduced very strong clinical, anatomical, and experimental evidence to buttress their conception that oxygen want is of prime importance in producing the damage to the liver that results from heart failure. However, there is no reason to believe that it is the only factor operating. The retardation of blood flow through the liver presumably has deleterious consequences for the metabolism of the liver cells other than those due to oxygen lack, and the mechanical compression of the liver cells by the dilated capillaries (page 251) may also be of significance

2. Increase in the Production of Bilirubin.—There is good reason to believe that this factor is often an important adjuvant to the depression of liver function in causing the hyperbilirubinemia and jaundice of heart failure Clinically, the patients exhibit increased excretion of urobilin in the stools (Eppinger[7]) and of urobilinogen in the urine The greatest amount of blood destruction probably occurs in the lung This is indicated by the expectoration of heart failure cells and by the brown hemosiderin pigmentation (brown induration) seen at necropsy, which testify to the destruction of stagnated and extravasated erythrocytes in the lungs. The deposition of hemosiderin in the lungs is most often diffuse, which shows that it is not only in infarcts that destruction of red cells occurs Peculiarly enough, the liver and spleen contain very little hemosiderin in uncomplicated heart failure (Lubarsch[19]).

3. Diminution in Blood Flow Through the Liver.—When heart failure results in diminished cardiac output, it is to be presumed that the volume of blood passing through the liver per minute is also diminished. This is another factor, though doubtless only an accessory one, which tends to cause retention of bilirubin in the blood.

To Summarize.—Cyanotic icterus is due primarily to impairment of the excretory function of the liver. Accessory factors are

increase in the production of bilirubin and diminution in the volume of blood flow through the liver.

In accord with his classification of jaundice into retentional and regurgitational, Rich[29] recognized two forms of cardiac hyperbilirubinemia and icterus: When the changes in the liver cells are confined to central atrophy and fatty deposition, there is pure *retentional jaundice* and the Van den Bergh reaction in the blood is indirect. But when the damage to the liver is so severe as to produce necrosis of the liver cells, there is regurgitation of bile from the ducts into the blood, and this *regurgitational jaundice* is evidenced by a direct Van den Bergh reaction in the blood and very rarely by the appearance of bile acids in the urine.

THE SPLEEN

The spleen is very inconspicuous in the symptomatology of heart failure. Apart from the very exceptional instances in which secondary changes in the liver cause significant obstruction to blood flow through this organ, it seems doubtful if the spleen is ever sufficiently enlarged to be palpable as a result of uncomplicated heart failure.

The appearance of the spleen at necropsy varies with the duration of the insufficiency of the right heart In instances of acute heart failure, or those of relatively recent inception, the spleen is slightly enlarged, more so in thickness than in length or breadth It is dark bluish-red or purple in color and feels firm or rubbery (cyanotic induration). On section, it holds its shape even though a considerable amount of blood escapes from the vessels Microscopically, the most prominent feature is distention of the venous sinuses, which are gorged with red blood cells While there may be some increase in the number of erythrocytes in the pulp, this is not a prominent feature unless there is complication by splenic tumor due to infection.

The anatomical findings are different in cases of long-standing heart failure Here the spleen is often decreased in size (cyanotic atrophy), weighing but 80 to 100 grams The organ feels hard. The capsule is thickened, opaque, and often wrinkled On section, the spleen cuts with resistance and reveals thickening of the trabeculæ *and blood vessels. Microscopically, the venous sinsuses are* seen to be distended and their walls thickened The connective-tissue framework of the organ is greatly thickened. The atrophic pulp contains very few red cells and usually little iron is revealed by appropriate stains.

The pathogenesis of cyanotic atrophy of the spleen has not been entirely elucidated. It is possible that it is due to the same variety of connective-tissue hyperplasia that occurs in consequence of

chronic passive congestion in various organs But another factor may also enter because of the reservoir function of the spleen. Patients with long-standing cardiac insufficiency generally have an increased circulating blood volume. Such increase in circulating blood volume probably implies an emptying of the blood depots, of which the spleen is the classical example (page 62), into the general circulation That this actually occurs is indicated by the paucity of red cells in the pulp of the spleen of such patients with long-standing heart failure, despite the engorgement of the venous sinuses The long-continued empty state of the splenic reservoir may well lead to atrophy of the organ with hyperplasia of the connective tissue framework If this hypothesis (for such is all it is) is true, two opposing influences act on the size of the spleen in heart failure (1) Engorgement of the veins, tending to increase the size of the organ and predominating in the early stages, and (2) emptying of the blood reservoir, tending to decrease the size of the spleen, and predominant in long-standing cases.

Two other influences occasionally enlarge the spleen of patients with heart failure sufficiently to render it palpable. The first of these is infection. In exceptional instances of rheumatic heart disease, I have been able to palpate the spleen during bouts of active rheumatic fever. The second is the development of marked atrophic and fibrotic changes in the liver (cardiac cirrhosis) as a result of long-standing right heart failure. In some, though by no means all, cases of this type, the spleen is considerably enlarged and can be felt Since these cases generally have recurrent ascites, Laennec's cirrhosis may be simulated It is probably the increased resistance to blood flow through the liver in these instances of "cardiac cirrhosis" that leads to the splenomegaly and ascites through the intermediacy of portal hypertension. The splenomegaly in adhesive mediastino-pericarditis is discussed in Chapter XXX Rarely a large effusion in the left pleura due to heart failure pushes the spleen down sufficiently to render it palpable, although the organ is not enlarged The splenomegaly of subacute bacterial endocarditis is not due to heart failure but to hyperplastic processes correlated with the infection and to infarction

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CHAPTER XVI

THE KIDNEYS AND URINE

THE urine is the mirror of the circulation through the kidneys. The volume and composition of the urine are far more intimately related to the velocity and pressure of the blood as it traverses the renal capillaries than are the saliva, sweat, pancreatic juice, and other true secretions to the corresponding mechanical coefficients of the circulation through the organs in which they are produced. For this reason, observation of the urine is one of the most valuable means at the disposal of the clinician for evaluation of the circulatory status. A glance at the urinal with its scanty, high-colored urine often suffices to reveal the presence of heart failure, while abundant, pale urine may immediately indicate that digitalization or some other therapeutic measure is accomplishing the desired object. Of especial value in patients with circulatory failure is the comparative observation of the daily urinary volumes, especially when considered in conjunction with the fluid intake and the fluctuations in body weight.

This chapter will be limited to the renal manifestations of those forms of circulatory failure which are characterized by engorgement of the systemic veins, *i. e.*, right heart failure and hypodiastolic failure. Parenthetically, it may be mentioned here that the elaboration of the urine is also affected by other forms of circulatory insufficiently. Thus, in isolated left heart failure without venous engorgement I have repeatedly observed oliguria as low as 400 or 500 cc. daily with urine of high specific gravity. With improvement of the left heart, the urinary volume rises. However, I have not observed the oliguria of left heart failure to be accompanied by albuminuria or any of the other characteristics of the urine in passive congestion of the kidneys And even oliguria is not always definitely demonstrable in left heart failure; patients with severe exertional dyspnea and paroxysms of cardiac asthma may eliminate 1000 cc. of urine or more during the day. It is to be presumed that the oliguria of left heart failure is a result of diminution in the volume of blood flow through the kidneys, for it may be present when the arterial pressure is normal. In peripheral circulatory failure, oliguria occurs and may even attain anuria (page 623).

PATHOLOGICAL ANATOMY OF ENGORGEMENT OF THE KIDNEY

The engorged kidney is enlarged. Usually the increase in size is but moderate and consists largely in an increment in thickness, but exceptionally the engorged kidney weighs almost twice the

normal. It feels firm and is sometimes actually hard. The capsule is thin and strips readily, without occasioning loss of kidney substance. The surface is smooth and dark red to purple in color. Occasionally, in cases of considerable duration, there is a yellowish mottling The stellate veins are distended and prominent. On section, cortex and medulla are well differentiated, the former being of somewhat the same color as the surface, the medulla darker, occasionally almost black, and with prominent striation due to the distended straight veins In long-standing cases, there is often marked yellowish discoloration of the cortex due to fatty change. Often, the glomeruli are enlarged and form quite prominent bright red dots, but in other cases they are hard to make out. The pelvis is engorged.

Microscopically, the distention and engorgement of the veins and capillaries is the most striking feature; indeed, in recent cases there may be little further abnormality. Quite often, the engorgement of the intertubular capillaries is much more marked than that of the glomerular loops. I have several times seen sections from cases of right heart failure of recent inception in which the intertubular capillaries were markedly engorged, while the number of red cells in the glomerular loops seemed hardly increased. With longer engorgement, however, the Malpighian corpuscles also generally become intensely congested But there are also instances of long-standing passive congestion in which the engorgement of the glomerular capillaries is much less than that of the intertubular vessels, which Fahr[3] attributes to swelling of the walls of the glomerular loops.

Passive congestion soon leaves its marks on the specific renal elements. Coagulated protein and red cells are seen in some of the capsular spaces and the lumens of the tubules Especially the cells of the proximal convoluted tubules, but also other portions of the tubules, exhibit such regressive changes as cloudy swelling and the appearance of Sudan-staining fat Some desquamation occurs but this process is not prominent The occasional swelling of the walls of the glomerular loops was mentioned above Brownish pigment, usually small in amount, may be deposited in the tubular cells, especially those of the loop of Henle.

In chronic cases, there may be considerable atrophy of the cells of the convoluted tubules with collapse of some of the units; the latter change, however, is not widespread. With this, there may be considerable hyperplasia of the intertubular connective tissue. While the latter processes lead in rare, very chronic cases to scattered depressions of the surface of the kidney and are accompanied by marked induration of the organ, they do not produce any considerable contraction of the organ. It does not appear to have been established that chronic passive congestion *per se* ever leads

to a contracted kidney. The cases that were described as such by Schmaus and Horn[11] and other older investigators are evidently instances of the arteriosclerotic contracted kidney of essential hypertension complicated by heart failure.

THE URINE IN PASSIVE CONGESTION OF THE KIDNEYS

Volume.—The urinary volume is diminished in passive congestion of the kidneys. Oliguria is often a very early sign of cardiac insufficiency. The observant patient may notice and mention spontaneously that he passes little urine during the day, although he is thirsty, drinks considerably, and is able to be up and about without much dyspnea and little or no pitting edema of the feet. Many cardiac patients pass only 400 to 500 cc. of urine daily for weeks or even months. For a few days at a time, even smaller volumes may be eliminated, and in cardiac shock (page 653) there may be complete anuria. In a general way, the urinary volume varies inversely with the other evidences of circulatory failure. Of course, this relation may be disturbed by many of the complications that occur during cardiac failure. Thus, the development of bronchopneumonia or another febrile state may intensify the oliguria even though the circulatory status is not affected. On the other hand, in the very common cases in which heart failure supervenes in an individual with high blood pressure whose renal function has been impaired by arteriolosclerosis of the kidneys, the urinary output is often larger than would be expected from the other evidences of cardiac insufficiency. Indeed, when the fluid intake is not restricted, the daily urinary volume in such patients may be well above 1200 cc. despite increasing edema, swelling of the liver, etc. But comparison of the urinary output with the compensatory polyuria present before and after the episode of decompensation shows that the latter was accompanied by relative oliguria. Moreover, in such cases the specific gravity of the urine is not as high as is usual in heart failure, offering a further valuable indication of the reason for the absence of oliguria. In some instances of well-marked heart failure in thyrotoxicosis, also, the urinary volume may be maintained at practically a normal level, apparently as a result of the increased metabolism. The alleviation of polyuria in diabetics with arteriosclerosis or of nocturia in prostatics, is sometimes not a favorable sign but rather a result of cardiac weakness.

Two of the outstanding characteristics of cardiac oliguria are the pronounced effect of posture on the volume of urine and the delay in the urinary elimination of ingested fluid.

Orthostatic Oliguria and Nycturia.—Characteristic of the oliguria of cardiac weakness, especially in the incipient stages, is that it is decidedly *orthostatic* in nature. While the patient is up and about,

he passes little urine. But when he goes to bed at night he eliminates a correspondingly larger volume of urine, and consequently has to get up once or twice, or even more, to pass urine. While the healthy person, as a result of the prompt elimination of the water that is ingested and that which is formed in metabolism, eliminates much more urine during the day than during the night, this relation tends to be reversed in the patient with heart failure, a phenomenon that was termed nycturia by Péhu.[8] The cause of the nycturia of heart failure is evidently the accumulation of occult or manifest edema in the lower extremities during the day when the patient is up and about, so that during this time less water reaches the kidney for elimination. At night, when the patient assumes the recumbent posture, the venous engorgement of the lower extremities is diminished with the result that edema fluid is resorbed into the blood stream and eliminated as urine It is possible that an accessory factor in the orthostatic oliguria of some cardiac patients is increased resistance to the venous return from the kidneys themselves in the erect posture, such as occurs in individuals with orthostatic albuminuria

The differentiation of nycturia due to heart failure from that which results from renal insufficiency is important, especially for rational therapy. It is usually readily accomplished by observation of the specific gravity of the urine. In cardiac nycturia, the specific gravity of the urine is high The nycturia of renal insufficiency, on the other hand, is a corollary of the inability of the kidney to form concentrated urine The result of the low concentration of the urine is that polyuria is necessary to eliminate the katabolites, and the kidney continues to form urine at a more or less uniform rate throughout the twenty-four hours, with consequent nocturia. In such patients, the specific gravity of the urine is low and is thus differentiated from that in cardiac nycturia Moreover, in renal insufficiency the total twenty-four-hour urinary volume is increased and not decreased as is the case in cardiac nycturia And finally the individual with renal insufficiency has polyuria during the day, while in heart failure little urine is eliminated while up and about

Delayed Urinary Elimination.—Another manifestation of the oliguria of heart failure is the delay in the urinary elimination of ingested water. If a healthy person drinks 1200 cc. of water or lemonade in one-half hour, it is eliminated within four hours, the larger half within the first two hours. This is not true of patients with heart failure, who pass only a fraction of the ingested water in the urine of the first four hours, and the amount eliminated is considerably smaller if the subject sits up during the test. The causes of the delayed elimination will be discussed below. In patients with hypertensive heart disease, it should be borne in

mind that delayed water excretion may be due to either cardiac or renal insufficiency. The significance of the two factors can be evaluated by the concentration test. If the patient is able to elaborate urine of high specific gravity, the defective water elimination is due to heart failure On the other hand, if the maximum specific gravity of the urine is low, there is renal insufficiency. But it should be remembered that in the presence of severe impairment of renal function, the urine remains of low specific gravity despite complication by heart failure.

One of the most valuable signs of improvement in a patient with heart failure is increase in the volume of urine When an individual with cardiac edema starts to improve, either spontaneously or as a result of digitalization, polyuria appears and may amount to even 3000 or 4000, cc daily until the retained water is eliminated It was because of this phenomenon that digitalis attained its original reputation as a diuretic.

Mechanism of Cardiac Oliguria.—At least two main mechanisms come into consideration in the pathogenesis of cardiac oliguria: (1) primarily extrarenal retention of water in the tissues so that less is available to the kidneys for excretion; (2) decrease in the capacity of the engorged kidney to excrete water.

1. *Extrarenal Factors* —In the section on the pathogenesis of cardiac edema (page 192), we have seen that the retention of water in the tissues which occurs in right heart failure is due to extrarenal causes (primarily increase in capillary pressure, secondarily heightened permeability of the capillaries and decrease in colloid osmotic pressure of the blood) As a result of the operation of these factors, water is displaced from the blood stream into the tissue spaces. The consequence is that less water is available for the kidneys to excrete and oliguria results just as it does in consequence of profuse perspiration or abundant vomiting.

That extrarenal factors and not the kidney are primarily responsible for the oliguria of heart failure is also shown by the fact that when fluid is rapidly mobilized into the blood stream of such patients, it is excreted quite rapidly. Thus, when cardiac insufficiency results in marked edema of the lower extremities, elevation of the latter is often followed by pronounced increase in urinary output. And similarly, as mentioned above, the urinary volume rises when a patient with cardiac oliguria assumes the recumbent posture. It has also been found repeatedly that, while an individual with cardiac oliguria eliminates in the urine of the next few hours only a small part of any considerable volume of salt solution that he drinks, the intravenous injection of the same volume of salt solution is followed by prompt increase in urinary volume (Nonnenbruch[7]) Further evidence of the primarily extrarenal causation of cardiac oliguria was brought forward by Volhard,[18]

who observed that in cardiac patients the red cell count rises during oliguria and falls during diuresis. This is, of course, the reverse of what would be expected in renal retention of water

All these observations indicate the primarily extrarenal origin of cardiac oliguria. Indeed, the copious diuresis that salyrgan produces in most instances of cardiac edema points in the same direction, for a similar response is not usually obtained in oliguria due to renal insufficiency.

2. *Renal Factors.*—It has been seen that cardiac oliguria is due at least principally to fluid retention of extrarenal origin, and that the engorged kidneys are able to increase the volume of urine if more water is rendered available for excretion by mobilization into the blood stream from the tissues in which it is retained Whether or not the capacity of the kidney to excrete water is diminished by passive congestion remains to be determined The many animal experiments that have been performed in the effort to elucidate the mechanism of the formation of urine have shown that impediment to the venous return from the kidneys usually diminishes the volume of urine (Cushny[2]) However, this is not invariably the case Rowntree, Fitz and Geraghty[10] found that when they produced partial obstruction to venous return from one kidney by putting a band around the renal vein, in *exceptional* instances a larger volume of urine was formed by the congested kidney In these experiments, it would seem that the increased filtration pressure more than overcame the effect of the slowing of blood flow so that the volume of urine increased However, the more usual effect of partial obstruction of the renal vein in animal experiments seems to be that the slowing of blood flow outweighs the increase in filtration pressure, with resultant decrease in the volume of urine. Whether slowing of flow or increase in capillary pressure dominates in the passive congestion of human heart failure has not been demonstrated. Moreover, in heart disease these mechanical factors are complicated sooner or later by the damage to the kidney cells that results from the defective circulation, one of the manifestations of which is albuminuria It is generally taken for granted that such damage to the renal cells diminishes the volume of urine, presumably through injury to the glomerular filter, a conception that would seem well supported by the histological appearance of the Malpighian bodies (page 265). On the other hand, the tubular cells also suffer from impaired nutrition, and the possibility is to be borne in mind that impairment of their resorptive function may tend to increase the volume of urine. However, the usual high specific gravity of the urine in passive congestion indicates that tubular resorption is quite efficient.

It would thus seem that much remains to be learned about the effect of passive congestion on the ability of the kidneys to excrete water. In any event, the evidence presented above seems to

indicate strongly that the oliguria of right heart failure is due at least predominantly to extrarenal factors, and that the engorged kidneys are able to increase their output considerably as correspondingly more water is mobilized into the blood stream.

Appearance.—The urine formed by the engorged kidney is dark; when the oliguria is severe, it attains a brick-red or brown color. When first passed, the urine is clear, but as it cools urates and uric acid settle out, so that the transparency diminishes and a copious sediment* resembling brick dust is deposited at the bottom and adheres to the sides of the glass (*sedimentum lateritium*). The color of the sediment is due to adsorption on the urates and uric acid of the urinary pigments which are present in high concentration. If the urine is warmed to body temperature or alkalinized, the urates dissolve and the urine becomes clear again

The color of the urine is darker than corresponds to the specific gravity, high though the latter is. This increased pigmentation of the urine in heart failure has been studied quantitatively and in great detail by Heilmeyer[4] by means of the photometer. He has found that in addition to the increased content of the urine in urobilinogen, the other urinary pigments are also increased Heilmeyer[4] believes that the increased pigment content of the urine in heart failure is largely a result of damage to the functions of the liver. However, in those cases in which there is increased blood destruction in the lung and other organs, this factor is doubtless also of significance According to the investigations of Heilmeyer and Sturm,[14] the increased elimination of urinary pigments is so constant in heart failure that the photometric study of the urine is a valuable means of evaluating the functional status of the heart.

With the polyuria of improvement from cardiac insufficiency, the urine becomes lighter and may be almost water-clear. Light urine is also encountered, despite heart failure, in renal insufficiency.

Specific Gravity.—The specific gravity of the urine is high, often remaining between 1 025 and 1 035 for days or weeks at a time. Even when the patient drinks large volumes of water, the specific gravity remains high because water is retained in the tissues and little excreted in the urine. But if diuresis is produced by salyrgan or another diuretic, the polyuria is accompanied by low specific gravity. Hinteregger[5] reports two instances of right heart failure in which the specific gravity of the urine was fixed around 1 010, but I have not observed this apart from complication by renal disease. When there is renal insufficiency, even the most severe heart failure may not result in elevation of the low specific gravity of the urine. The polyuria of recovery from heart failure is, of course, accompanied by low specific gravity.

* I have twice seen patients who passed numerous small uric acid calculi during episodes of heart failure, though they neither before nor after suffered from calculous disease

Normal Urinary Constituents.— *Urea* and *uric acid* are increased in concentration in the urine during the oliguria of heart failure. The urea content may even exceed 4 per cent. The increase in concentration corresponds to the diminution in urinary volume down to very pronounced degrees of oliguria, so that the total urinary output of nitrogenous bodies is not lessened. It is only when oliguria becomes extreme, about 300 cc. of urine daily, that nitrogen excretion falls behind the requirements of metabolism and the nonprotein nitrogen of the blood rises

The same is not true of the *chloride* excretion in the urine. The concentration of chloride in the urine is not increased in proportion to the high specific gravity and oliguria; on the contrary, it is often low, and while edema is forming may be present in only minute amounts. The result is, since the urinary volume is diminished, that the daily output of chloride in the urine is subnormal, and if any considerable amount of chloride is ingested it is retained in the organism. That the retention of chloride in heart failure is not due to inability of the kidney to excrete the ion is immediately proved in many of the cases with little chloride in the urine by the finding that the concentration of chloride in the plasma is subnormal. In these cases, the low chloride level in the plasma is doubtless responsible for the depression of excretion of the ion in the urine When the plasma chloride concentration is low in heart failure, this is probably at least largely a consequence of increased transudation from the capillaries. For, in accord with what would be anticipated on the basis of the Donnan equilibrium, the edema fluid, having a lower protein content than the plasma, has a higher concentration of chloride than the latter. The result is that disproportionately more chloride than water is removed from the plasma Retention of water and of chloride in heart failure are thus two aspects of the same process, and any of the circumstances which lead to the mobilization and elimination of edema fluid also cause a corresponding outpouring of chloride. During copious salyrgan diuresis in heart failure, as much as 30 or 40 grams of sodium chloride may be eliminated in the urine during twenty-four hours. Of course, factors other than the formation or resorption of edema also affect the level of chloride in the blood and consequently in the urine The result is sometimes high chloride concentration in the plasma and urine. According to the investigations of Peters, Bulger and Eisenmann,[9] the chloride content of the plasma in heart failure is influenced by that of bicarbonate They found that changes in the bicarbonate content of the blood (Chapter VII) tend to cause inverse changes in the chloride contention However, Peters and his associates observed that this reciprocal relationship between chloride and bicarbonate in heart failure—which is in line with what one would expect for the maintenance of electrolyte equilibrium—is often obscured by the intervention of other factors.

The *acidity* (hydrogen-ion concentration) of the urine in heart failure is usually high

The increase in the *total pigment elimination* in the urine in right heart failure has already been mentioned. The *urobilinogen* content of the urine varies, and is probably largely dependent on the extent to which liver function is impaired by the heart failure. The amount of blood destruction, especially in the lungs, is doubtless also significant in determining the urobilinogen content of the urine. More than one-half of Jolliffe's[6] patients with right heart failure showed increase in the elimination of urobilinogen in the urine. Schmitz and Sherman[12] also found that in children with right heart failure due to rheumatic fever, the urobilinogen content of the urine is not invariably increased and bears no constant relationship to the degree of the failure. They also observed that in children with rheumatic heart disease, increased excretion of urobilinogen may occur in the absence of heart failure—an observation which can, of course, be made in various fevers.

Pathological Constituents.—Albuminuria is a common manifestation of passive engorgement of the kidney, though not invariably present It usually does not appear until the engorgement has existed for several days, and on the other hand may persist for some time after increase in urinary volume shows that the congestion of the kidneys has been relieved Most often, the albuminuria is but slight, amounting to less than 0.1 per cent. But in exceptional instances, especially in older persons who presumably have some renal arteriosclerosis, heart failure may result in much more marked albuminuria; the connection of the latter with the cardiac failure is shown by the fact that it diminishes or disappears with the other symptoms of heart failure when digitalization or other measures are successful. In essential hypertension, also, heart failure may be accompanied by massive albuminuria It is said that the urinary protein in heart failure consists of more globulin than albumin (Cloetta[1]), but the reverse was true in the only two cases studied by the writer

Examination of the sediment often reveals casts, red blood cells and white blood cells; usually, they are not numerous, but exceptionally they are quite abundant Stewart and Moore[13] counted the formed elements in the urine of patients with heart failure, they found that the average number of casts was 60 times and that of red and white blood cells 10 to 15 times greater than in health. While most of the casts are hyaline, granular and epithelial elements are commonly found. That these formed elements occur in the urine as a result of passive congestion alone is to be emphasized, in themselves, they offer no justification for the diagnosis of complicating inflammatory or embolic lesions The frequent abundance of urates and of uric acid crystals in the urine in right heart failure has already been mentioned.

RENAL FUNCTION

Impairment of renal function is evidenced by diminution in the ability to form urine of high concentration. Consequently, *the high specific gravity of the urine that is produced by kidneys that are the seat of passive congestion constitutes prima facie evidence that renal function is unimpaired.* Almost invariably, unless there is combination with inflammatory or arteriosclerotic kidney disease, any random specimen of urine passed by a patient with heart failure has a specific gravity above 1.020 Or in the unusual instance in which this is not the case, the simple concentration test shows that the patient can form urine of specific gravity above 1.020 and therefore has adequate renal function.

The *urea concentration test* also shows that renal function is unimpaired, for the urine contains a high concentration of urea

Excretion of *phenolsulphonephthalein* is sometimes, though not always, diminished in severe right heart failure When the kidneys are severely engorged and there is marked oliguria, the output of the dye in two hours may be less than 10 per cent However, as the high concentration of the urine shows, the diminished excretion of phenolsulphonephthalein is not due to impaired renal function, it results from the oliguria and the slowing of blood flow

The *urea clearance test* of Van Slyke often gives results within the range of the normal in heart failure. But when the engorgement of the kidneys is severe and the oliguria extreme, definitely subnormal results are not unusual This is due to the oliguria

If the patient with right heart failure drinks a large volume of water (*dilution test*), the water is excreted far more slowly than in health Thus, if 1200 cc. of water are taken within one-half hour, instead of passing practically the entire amount or more within four hours as does the healthy person, the individual with heart failure may eliminate only about 200 cc And the specific gravity of the urine may not fall below 1 015 or even more, instead of the normal 1.004 or less. Similarly, sodium chloride is excreted but slowly. The water and salt retention is, of course, not due to impairment of renal function but is a consequence of the extrarenal disturbances described in Chapter XII, which cause water and salt to be retained in the tissue spaces

The *non-protein nitrogen* and *urea* concentrations in the blood are not elevated in the large majority of instances of heart failure, though the tendency is for the values to approach the upper limit of normal. However, in cases in which oliguria is intense, the urinary volume falling below about 500 cc. daily for several days, considerable nitrogen retention may occur. The human kidney cannot excrete urea in higher concentration than about 5 per cent. If, therefore, less than 300 cc. of urine are eliminated daily and the production of urea exceeds 15 grams in the twenty-four hours,

retention must occur. Nevertheless, it is extremely rare for the non-protein nitrogen of the blood to attain 100 mg. per cent in the course of protracted cardiac insufficiency. The reason is that oliguria of the necessary severity and duration is rare other than terminally in such cases. On the other hand, in the acute heart failure of myocardial infarction the cardiac output and consequently renal blood flow is reduced to values so low that extreme oliguria and even anuria may occur, with resultant azotemia of high degree. The same mechanism often leads to pronounced nitrogen retention in peripheral circulatory failure (page 623).

When heart failure complicates renal disease, nitrogen retention often occurs The most common cases of this type are in individuals with essential hypertension and impairment of renal function as a result of arteriolosclerotic changes in the kidneys. Nitrogen retention may first appear in such cases when the heart weakens. The reason for the nitrogen retention is that the arteriolosclerotic kidney is unable to form urine of sufficiently high concentration to compensate for the diminution in urinary volume due to the heart failure The cardiac factor in such cases is revealed by the fact that the non-protein nitrogen of the blood rises despite urinary specific gravity as high as 1.015 or 1.018 And the non-protein nitrogen of the blood may fall to normal with improvement of the heart

SUBJECTIVE SYMPTOMS AND PHYSICAL SIGNS OF RENAL ENGORGEMENT

Despite the enlargement of the kidney and the stretching of the capsule, passive engorgement of the organ does not cause pain. Nor is there tenderness on palpation or on deep percussion in the costovertebral region The occurrence of pain or tenderness indicates an inflammatory or embolic complication. The enlargement of the kidney in chronic passive congestion is not sufficient to be determined by palpation

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CHAPTER XVII

THE CENTRAL NERVOUS SYSTEM

AMPLE blood supply is indispensable to the central nervous system. Experimental investigations long ago showed that interruption of the blood flow through the brain quickly results in stimulation or depression, the most conspicuous phenomena generally being due to these effects on the cortex or the vital centers in the brain stem. At first blush, therefore, it is surprising that nervous symptoms are not more conspicuous in the clinical picture of circulatory failure than is actually the case Presumably, the relative paucity of nervous symptoms until the late stages is correlated with the supreme importance of the master organ of the body, mechanisms being available (pages 292 and 631) which serve to maintain tolerable circulation through the brain despite circulatory failure which has made itself very evident in other parts of the organism.

Nevertheless, the central nervous system does not escape altogether unscathed even in early circulatory failure *It is possible* that slowing of cerebral blood flow plays some, though probably only an accessory rôle in the pathogenesis of some instances of cardiac dyspnea (page 135). And when Cheyne-Stokes breathing appears in circulatory failure, it is largely a result of the disturbed blood flow through the medulla (Chapter IX) However, the relatively unusual occurrence of Cheyne-Stokes breathing in uncomplicated circulatory insufficiency, and the late stage at which it appears, if at all, are in themselves evidences of how well the circulation through the brain stem is maintained in circulatory failure.

In addition to these respiratory disturbances, which have already been considered, various other nervous symptoms may occur in circulatory failure:

1 Symptoms of cerebral ischemia due to sudden decrease in cardiac output, of which the classical example is the Stokes-Adams syndrome.

2. Psychoses and other mental manifestations occurring in protracted heart failure, and clearly a consequence of it, but of pathogenesis which is not yet clear.

3. Symptoms due to emboli originating in the thrombi that so often form in the dilated chambers of the failing left heart or over an infarct or aneurysm of the left ventricle. The cerebral emboli emanating from the vegetations of bacterial endocarditis are not correlated with heart failure.

4. Psychoneurotic symptoms due to the great effect that the consciousness of heart disease has on the psyche of many individuals

5. Cerebral symptoms due to the disease that causes the heart failure The most common example is the appearance of mental or other symptoms of cerebral arteriosclerosis in patients with hypertensive or arteriosclerotic heart disease. In such persons, I have several times observed that cardiac failure was followed by the appearance or exacerbation of cerebral symptoms; presumably, the diminution in *vis a tergo* intensified the circulatory disturbance in the brain due to the local arterial disease. Chorea or other cerebral manifestations of rheumatic fever may, of course, accompany rheumatic heart disease, but it is extremely rare for them to be conspicuous in the presence of cardiac failure. In right heart failure secondary to pulmonary disease, there may be somnolence due to anoxemia, which is largely the result of lesions in the lungs (page 289)

6 Nervous symptoms due to therapeutic agents, *e. g.*, morphine, aminophyllin, caffein, and digitalis (page 725). The development of psychoses during the resorption of edema will be mentioned below.

Before describing these clinical pictures, a few words on the direct effects of venous stasis on the central nervous system may not be out of place.

ANATOMICAL FINDINGS IN THE BRAIN IN RIGHT HEART FAILURE

In passive congestion, the brain is voluminous and fills out the dura. The veins of the brain and pia are engorged. The latter form a closely meshed, dark blue network. As a result of the distention of the intracerebral veins, numerous large blood points appear when the brain is sectioned and rapidly refill when washed off. However, it is not always easy to judge of the intravital blood content of the cerebral vessels from the postmortem appearance. If the necropsy of the thoracic organs is carried out before the skull is opened, the intracranial veins tend to empty. On the other hand, if the cadaver lies with the head down, the vessels of the dependent parts of the meninges and brain become engorged Intense engorgement of the intracranial vessels is the rule in asphyxial death, whatever the antecedent condition.

The leptomeninges are often thickened and edematous in chronic passive congestion. The brain is large and heavy. If there is much edema, it is very soft. On section, the edema is revealed by the moist surface and by the fact that the blood points due to the severed veins quickly flow away in the edema fluid. Rarely, the edema is so marked that the convolutions are flattened. The engorged brain substance may be bluish or brownish-red. Various

histological changes have been described in the ganglion cells, the medullary sheaths, and the axis cylinders of the engorged and edematous brain (Kauffmann[16]).

THE CEREBROSPINAL FLUID IN CIRCULATORY FAILURE

Elevation of pressure in the intracranial veins immediately results in rise in tension of the cerebrospinal fluid This is well illustrated by the familiar Queckenstedt maneuver, in which compression of the jugular veins is followed by increase in subarachnoid pressure. Since the latter returns to normal as soon as jugular compression is discontinued, the rise is obviously due to engorgement of the intracranial tributaries of these veins. High pressure of the cerebrospinal fluid also results from compression of the superior vena cava by mediastinal masses.

In view of these facts, it is not surprising that high venous pressure due to right heart failure results in elevation of the tension of the cerebrospinal fluid (Tzanck and Renault,[29] Harrison[11]) Friedfeld and Fishberg[10] found that as the venous pressure rises in right heart failure, the pressure of the cerebrospinal fluid also mounts to such an extent that it is higher than the venous pressure The result is that in patients with venous pressure of over 30 cm. of water, the pressure of the cerebrospinal fluid may exceed 45 cm of water. When the venous pressure falls during recovery, the cerebrospinal pressure also drops. However, there is usually a lag after the venous pressure has returned to normal levels before the intraspinal pressure drops to its usual height This lag is probably due to the fact that the rise in cerebrospinal pressure results not only from engorgement of the intracranial veins but also, to a lesser extent, from edematous swelling of the brain Friedfeld and Fishberg found no evidence of any considerable increase in the volume of the cerebrospinal fluid in patients with high intraspinal pressure due to heart failure. Despite the fact that the tension of the cerebrospinal fluid often exceeds 30 or even 40 cm of water in right heart failure, the characteristic symptoms of increased intracranial pressure and papilledema do not appear. Friedfeld and the writer found no correlation between headaches in cardiac patients and the height of the intraspinal pressure

In left heart failure with normal venous pressure, the tension of the cerebrospinal fluid is normal In peripheral circulatory failure (shock) with its low venous pressure, the intraspinal tension is low.

SYMPTOMS DUE TO PAROXYSMAL CEREBRAL ISCHEMIA

It is possible that the inability to concentrate, ready fatigue during intellectual tasks, forgetfulness, and other mental symptoms which are among the banal complaints of intelligent cardiac patients

are at least partially attributable to diminution in blood flow through the brain. However, that such is actually the pathogenesis of these symptoms is not established; they also occur in various conditions in which the circulation is unimpaired. It is only when transitory episodes of diminution in cardiac output occur that the symptoms of diminished blood flow through the brain are clear cut. Indeed, because of the great sensitiveness of the brain to diminution in blood flow, the cerebral symptoms may be the only subjective manifestations of transitory decrease in cardiac output.

The symptoms resulting from paroxysmal decrease in the output of the left ventricle vary, naturally, in accord with the degree and duration of the diminution in cardiac accomplishment. On the other hand, the cerebral symptoms may be brought on, not by paroxysmal diminution in the efficiency of the heart, but by sudden increase in the work necessary to maintain the cerebral circulation. It is for this reason that the milder cerebral symptoms are especially apt to occur when the patient suddenly stands up,* starts to walk, becomes excited Obviously, cerebral arteriosclerosis renders the brain a *locus minoris resistentiæ* in the circulation, which would seem to be the reason that these symptoms are most common when heart failure co-exists with arterial disease.

Often, the mildest episodes are elicited only by specific questioning. They are variously described as momentary faintness, weakness, giddiness, black or fog before the eyes, a sensation that the floor is falling away, etc. The bystander may note a sudden pallor of the face and the patient may stop in the midst of a conversation or stagger, to prevent himself from falling, he grasps some object or sits down, and the incident is over. In other instances, the cerebral eclipse lasts longer the consciousness may be lost, either momentarily or for several minutes Occasionally, the patient falls and may injure himself. Focal cerebral phenomena, such as described by Barnes[2] in paroxysmal tachycardia (page 282), occur on rare occasions

When the cerebral anemia is more complete or more protracted, apoplectiform or epileptiform seizures may occur. While they may result from any of the causes of cerebral anemia described below, they are so rare apart from the Stokes-Adams syndrome that they will be described in connection with the latter. In the days when copious blood-letting was in favor, such attacks were not rare as a result of the cerebral anemia thus induced.

The clinical conditions in which circulatory failure may induce paroxysmal cerebral ischemia are the following:

* One of the Stokes'[17] original patients with Stokes-Adams syndrome could avert the attack, when the premonitory symptoms had appeared, by getting on his hands and knees with his head down

Heart Block.—The Stokes-Adams syndrome furnishes the outstanding example of paroxysmal cerebral ischemia due to diminution in the output of the left ventricle This syndrome is most often due to organic lesions of the bundle of His with resultant impairment of conduction and slowing of the ventricles However, there are also very rare instances of the syndrome of apoplectiform or epileptiform seizures accompanying slow pulse which are not the result of structural alterations in the heart but due to changes in the brain which stimulate the vagus and thus inhibit the heart sufficiently to produce symptoms of cerebral ischemia, these cases will be discussed in connection with vagal inhibition.

It is to be emphasized that the full-blown Stokes-Adams syndrome with convulsions is a rarity, and many patients with complete heart block live for years and decades without experiencing such seizures. The stroke volume is increased sufficiently to maintain the minute volume of the heart at a level, despite the slow rate, sufficient to avert cerebral ischemia. Electrocardiographic investigations have shown that the actual Stokes-Adams attacks in patients with heart block are precipitated by one of two mechanisms:

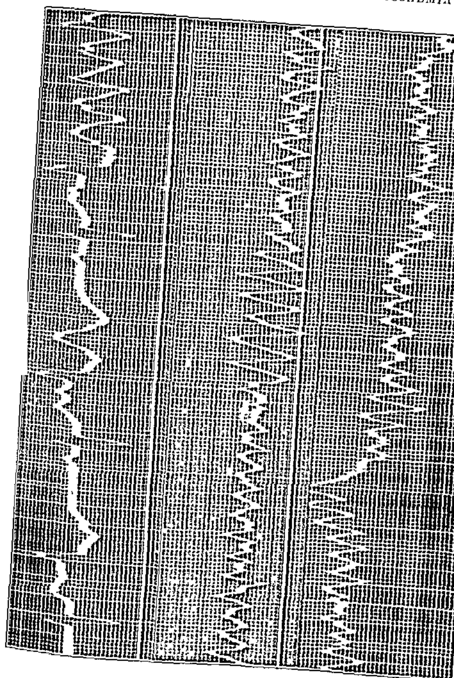
1. What seems to be much the more common mechanism is a decrease in the ventricular rate below that present between attacks, and which attains ventricular standstill of longer or shorter duration Such episodes of ventricular standstill are most common in heart block of recent inception, at which period the degree of block commonly fluctuates. When the block suddenly becomes much more severe or complete, an interval may elapse before the part of the ventricle with the most highly developed automaticity starts to function as the ventricular pacemaker, and at first the resultant idioventricular rhythm may be very slow. It seems to be during this period that the Stokes-Adams attacks are most apt to occur. After the heart block has become stabilized and the ventricular rate varies little over long periods, episodes due to cerebral ischemia are rarities The cause of the transitory increase in the severity of the auriculo-ventricular block which often leads to the paroxysm is not clear In some instances, the attack is preceded by a pulse rate unusually high for the patient, and it is possible that this increased task exhausts the already depressed bundle with the result that it no longer functions until it has had a sufficient rest period. But in many cases there is no such preliminary increase in rate. It is possible, though purely hypothetical, that the actual Stokes-Adams seizures in patients with heart block due to organic lesions of the bundle of His result from reflex vagal inhibition. Indeed, Vaquez and Esmein[30] consider that the reason Stokes-Adams attacks are more common in the early stages of heart block is that at this period paroxysmal vagal inhibition may come

into play, while later the lesion is so complete as to shelter the ventricle from the vagus

2. Much more rarely, the Stokes-Adams attack results from *paroxysmal ventricular fibrillation in a patient with heart block.* A number of such cases have been reported since the pioneer observation of Kerr and Bender[17] and I have observed one. The patient observed by Schwartz and Jezer[27]—to whose paper the reader is referred for a detailed study of the subject—over a period of *four months had daily attacks of Stokes-Adams syndrome* due to paroxysmal ventricular fibrillation, and on one day had no less than 207 periods of unconsciousness. When the ventricles are fibrillating, their output is minimal, so that no pulse can be felt and cerebral ischemia results In the patient studied by Schwartz and Jezer, as well as in my observation, no heart sounds could be heard during the period of ventricular fibrillation, so that such attacks can be differentiated from those due to ventricular standstill only by the electrocardiogram

The nature of the symptoms in a Stokes-Adams attack naturally depends on the duration of the cerebral ischemia. When the ventricle stops for five seconds or less, there is usually only faintness and vertigo. Mackenzie[19] observed in one patient that when the ventricular standstill lasted ten seconds there was unconsciousness, while stoppage of seventeen seconds was followed by convulsions. In Schwartz and Jezer's patient with paroxysmal ventricular fibrillation, momentary loss of consciousness occurred when the pulse stopped for between eight and ten seconds, and convulsions developed when the pulse disappeared for at least twenty seconds.

In the mildest Stokes-Adams attacks, due to brief stoppage of the ventricles, the symptoms are those described above (page 277) as characteristic of transitory cerebral ischemia, and recovery is almost immediate. But if the stoppage is longer, the patient falls unconscious and may suffer injury. At first, the face is of cadaveric pallor —the rapidity of the blanching in previously ruddy individuals is sometimes remarkable—but then gradually becomes more and more cyanotic until it may be dark purple The veins in the neck swell mightily The respiration is often stertorous, like in cerebral hemorrhage, and Cheyne-Stokes breathing may develop There is sometimes conjugate deviation, and I have elicited the Babinski sign during the attack. Urine and feces may be passed involuntarily If the ventricle does not start to beat, the convulsive phenomena appear. The body stiffens and the muscles of the face and neck begin to twitch Then tonic and clonic convulsions implicate the upper extremities and may become generalized. Sometimes, the patient foams at the mouth like an epileptic. Such an attack may last from thirty seconds to several minutes, the longer seizures being rare. Especially in the more protracted



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Left or Right Ventricular Failure.—In patients suffering from left ventricular strain as a result of hypertension, aortic valvular defects, or coronary artery disease, the failure of the left ventricle may be documented by symptoms of cerebral ischemia. This is probably the mechanism of the vertigo and syncope that are quite common in individuals with aortic valvular defects In coronary thrombosis, the acute and severe left ventricular failure not uncommonly results in syncope, vertigo or other manifestations of cerebral ischemia. Indeed, on rare occasions the cerebral symptoms dominate the onset of myocardial infarction. I recently saw a man, aged twenty-nine years, who fell unconscious while at work, and the diagnosis of coronary thrombosis could not be definitely established until the electrocardiogram was seen. When left ventricular failure produces cardiac asthma with or without manifest pulmonary edema, there may be symptoms of cerebral ischemia, but these are usually overshadowed by the more conspicuous pulmonary manifestations. However, Dumas[5] has published such cases in which pulmonary edema was accompanied by syncope, coma, or convulsions; I have seen similar instances He mentions cases of acute left ventricular failure in which the cerebral symptoms so predominated in the clinical picture that the *intra vitam* diagnosis was cerebral vascular accident, and the pulmonary edema was first discovered at necropsy.

Acute *right ventricular failure* due to pulmonary embolism may result in syncope or other consequences of inadequate cerebral blood flow.

Vagal Inhibition.—Overactivity of the vagus may so inhibit the heart and diminish its output as to produce symptoms of cerebral ischemia Among the clinical conditions in which this occurs are the carotid sinus syndrome, neurocirculatory asthenia, some forms of organic heart disease, under the influence of digitalis, and in the neurogenic form of the Stokes-Adams syndrome.

The Carotid Sinus Syndrome —In a classical series of investigations, Weiss[33] and his associates have demonstrated that there exist states of pathological hypersensitivity of the carotid sinus which are responsible, through reflex mechanisms, for attacks of vertigo, syncope and even convulsions. Proof that these cerebral symptoms are due to a hypersensitive carotid sinus is obtained through reproduction of the clinical picture by pressure on the carotid sinus. Weiss was able to abolish the attacks by surgical denervation or anesthetization with procaine of the carotid sinus. Weiss and his co-workers find that, depending on which efferent pathway of the carotid sinus reflex arc is principally involved, *carotid sinus syncope*, as they term it, can be brought by three mechanisms, acting singly or in combination:

1 The *vagal type*, in which cerebral ischemia results from slowing of the heart due to vagal inhibition of the sinus node or depression

or auriculo-ventricular conduction which usually attains complete block for at least a few beats The administration of atropine or epinephrin abolishes the attack; the former acts by preventing vagal inhibition, the latter by stimulating the ventricles

2 The *depressor type,* in which cerebral blood flow is diminished as a result of the fall in arterial pressure produced by reflex vasodilatation reflexly mediated through the aortic depressor nerves. Atropine has no effect on the attacks because they are not due to vagal slowing, but they are terminated by the vasoconstriction of epinephrin Weiss found this type very rare

3. The *cerebral type,* due to neither slowing of the heart nor fall in arterial pressure, relieved by neither atropine nor epinephrin, and perhaps to be attributed to reflex cerebral vasoconstriction or stimulation of vegetative centers

For further details regarding the carotid sinus syndrome, a condition not uncommonly overlooked, the reader is referred to the above-mentioned papers of Weiss

Neurocirculatory Asthenia.—Episodes of giddiness or syncope are frequent in individuals of the constitutional type which is prone to manifest itself as what Oppenheimer[23] termed neurocirculatory asthenia and Lewis[15] the effort syndrome, this clinical conception probably includes what Eppinger and Hess[8] regarded as "vagotonia," a functional disturbance of the autonomic nervous system which hardly exists in uncomplicated form The attacks are not all brought on through the same mechanism In some, and this includes a large majority of the instances that I have seen, the pulse is not slowed, showing that they are not due to vagal predominance Often, a fall in blood pressure indicates that peripheral vasodilatation may be responsible for deficient blood supply to the brain and consequent faintness and other symptoms of cerebral ischemia In contrast to these attacks, persons with neurocirculatory asthenia may also suffer episodes of giddiness or syncope, or rarely even twitchings or convulsions, during which the pulse is very slow and may indeed be impalpable for several seconds. Such seizures evidently result from vagal inhibition of the heart. Cotton and Lewis[4] made a careful study of these attacks, which they brought on by the act of drawing blood This resulted in slowing of the heart and fall in blood pressure. The mechanism of the attacks was vagal inhibition of the whole heart, the electrocardiogram revealing sino-auricular block. The vagal origin of the episodes was further confirmed by the fact that they were relieved by atropine. In individuals who are subject to such seizures, they can often be evoked by pressure on the carotid sinus or eyeball

Organic Heart Disease and the Influence of Digitalis—It has long been known that in organic cardiac disease the heart is often especially susceptible to vagal inhibition. Robinson and Draper[25]

found that in auricular fibrillation pressure on the right carotid sinus usually causes marked slowing or stoppage of the ventricles. By the same procedure in children, they were sometimes able to produce complete auriculo-ventricular dissociation. Mackenzie[20] observed an individual with rheumatic heart disease in whom swallowing, doubtless through a vagal reflex probably initiated by a hypersensitive carotid sinus, produced transitory auriculo-ventricular block. The susceptibility of the bundle of His to vagal inhibition is especially great when its conductivity is already depressed by disease, by digitalis, or by experimental injury; under such circumstances, vagal stimulation may convert partial into complete auriculo-ventricular block, which can again be removed by the administration of atropine Patients with ectopic rhythms are sometimes strikingly susceptible to vagal inhibition, a phenomenon which occasionally stands the physician in good stead when he is able to restore normal rhythm by pressure on the carotid sinus or eyeball. Indeed, the sensitivity to vagal inhibition may be dangerously great; I recently witnessed a most disagreeable episode in a woman with auricular flutter in whom ocular pressure resulted in disappearance of the pulse for fifteen seconds with complete unconsciousness of about two minutes' duration The frequent hypersusceptibility of the diseased heart to vagal inhibition is probably at the root of some of the spontaneous episodes of syncope that occur in individuals with cardiac disease. An exquisite example was published by Wedd and Wilson,[21] who observed a person with permanent nodal rhythm in whom psychic influences elicited episodes of cardiac standstill or extreme bradycardia with consecutive cerebral phenomena, the cardiac standstill was the result of vagal overactivity, being prevented by atropine.

Marked slowing of the heart is often produced by carotid sinus or ocular pressure in individuals under the influence of digitalis. On page 694 it will be seen that there is evidence that digitalis has a direct sensitizing action on the carotid sinus. Weiss suggests that the sensitizing action of digitalis on the carotid sinus is sometimes concerned in the production of cerebral symptoms

The Neurogenic Form of the Stokes-Adams Syndrome.—The question has been repeatedly discussed whether lesions in the brain or along the course of the nerves regulating the action of the heart can produce, through the intermediacy of vagal inhibition of the heart, the clinical picture of the Stokes-Adams syndrome, *i e*, slow pulse with apoplectiform or epileptiform seizures. In one of the original cases of Morgagni,[22] who observed the syndrome before Adams, he detected no considerable cardiac lesions, and because of the presence of peripheral arteriosclerosis attributed the clinical phenomena to cerebral arteriosclerosis. Inasmuch as this was before the days of histology, and Morgagni did not even open the skull, no significance

can be attached to the claim either that the heart was intact or that a cerebral lesion was present Since then, however, a number of cases have been published in which tumors or other masses in the neck adjacent to the carotid sinus have been accompanied by attacks—coming on either spontaneously or induced by pressure—consisting of slow pulse and apoplectiform or epileptiform seizures. There have also been cases, though these are not as clear cut, in which tumors, varices and other lesions in the vicinity of the vagal nuclei in the bulb have been accompanied by the same clinical picture. (For casuistic references see Wenckebach and Winterberg[45] and Kahler[15]) The best studied case of such neurogenic Stokes-Adams syndrome is that reported by Weiss and Ferris[44] in which fainting attacks of ten years' duration usually incited by swallowing were associated with a diverticulum of the esophagus Distention of the esophagus with a rubber balloon reproduced the attacks, which were found to be mediated by complete auriculo-ventricular block and could be prevented by atropine. In another case reported by Flaum and Klima[9] Stokes-Adams attacks were also incited by swallowing and could be reproduced by pressure on the pyriform sinus and abolished by anesthetization of the larynx, here, the electrocardiogram showed the mechanism of the attacks to be bradycardia due to sino-auricular block.

In all the cases of neurogenic Stokes-Adams syndrome reported, the auriculo-ventricular dissociation has been intermittent, complete block in man is apparently always due to a change in the bundle of His and is not solely the result of vagal inhibition. This is not surprising, for experimental findings show that the heart always "escapes" before very long after the effects of vagal stimulation. However, as has been seen above, vagal inhibition can produce transitory impairment of conduction, especially when the bundle is already damaged, and may thus precipitate some of the cerebral episodes that occur in the course of cardiac disease.

Postural Hypotension.—Fainting or other symptoms of deficient cerebral blood flow may occur when an individual with postural hypotension arises Postural hypotension is a condition in which the normal vasoconstriction does not occur when the subject stands up, the result is stagnation of blood in the dependent parts, deficient venous return to the heart, and correspondingly decreased cardiac output Exquisite examples of postural hypotension are seen following splanchnic section for the treatment of hypertension (Allen and Adson[1]) as well as in some cases of tabes dorsalis and other diseases of the central nervous system (*cf* Ellis and Haynes[7]); in other instances, the etiology is obscure.

Shock.—In traumatic, hemorrhagic, postoperative and other varieties of shock, symptoms of cerebral ischemia are very common The deficient blood supply to the brain is one of the manifestations

of the decreased cardiac output resulting from the peripheral circulatory failure. The low arterial pressure is especially disadvantageous for the cerebral circulation in the erect posture. It is for this reason that the cerebral symptoms of shock are often alleviated when the head is kept low. The most common cerebral manifestation of shock is syncope. On rare occasions, epileptiform convulsions and such focal cerebral symptoms as amaurosis with intact pupillary reflexes occur, as I once saw in a patient with severe postpartum hemorrhage.

PSYCHOSES AND OTHER MENTAL SYMPTOMS DUE TO CIRCULATORY FAILURE

In the course of circulatory failure, various mental symptoms may occur. Most often, these are definitely psychoneurotic in nature (page 289). But in other cases the psychic manifestations are evidently a result of the circulatory disturbance in the brain. Such mental symptoms occur most often in protracted heart failure and, in their severe forms, almost always in the elderly The published observations seem to indicate that females are more often affected Many of the patients have well-marked cerebral arteriosclerosis but in the cases in question this has not caused evident mental changes until the circulation through the brain is further impaired by the supervention of cardiac weakness The appearance of psychoses during improvement and dehydration will be mentioned below. Wassermann[31] has found that severe mental disturbances in heart failure are very often associated with Cheyne-Stokes breathing; the explanation may be that this form of respiration is especially common in those with cerebral arteriosclerosis. It would seem probable that cerebral congestion and edema, as well as long-standing increase in cerebrospinal pressure, may be concerned in the production of the mental symptoms of heart failure. However, I am not acquainted with any investigation of the anatomical changes in the brains of such patients

Insomnia is a very common complaint of patients with heart failure. Its direct relation to the latter can often be demonstrated by the improved sleep as compensation is restored It is a symptom that should be taken very seriously in a patient who has not previously suffered from it, for on a number of occasions I have observed sleeplessness to be an early warning, especially in arteriosclerotic heart disease, of a turn for the worse In the late stages of heart failure, insomnia may be one of the most difficult symptoms to control.

Bad *dreams* are often a torture to the patient with heart failure Indeed, I have several times heard nightmares designated as the worst of the patient's tribulations. He often awakens terrorized

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Shock.—In traumatic, hemorrhagic, postoperative and other varieties of shock, symptoms of cerebral ischemia are very common. The deficient blood supply to the brain is one of the manifestations

psychoses following copious mercurial diuresis in cardiac patients, which cleared up completely. In fact, most of the so-called cardiac psychoses that I have seen have been in elderly individuals in whom treatment with digitalis, mercurial diuretics, and fluid and salt restriction had resulted in absorption of edema and diminution of other objective evidences of heart failure. Despite these evidences of "improvement," the patients were actually worse, being both cachectic and psychotic. In several such instances, the plasma chloride content was subnormal and improvement followed the cessation of digitalis and diuretics, and the administration of considerable amounts of water and sodium chloride. I believe that in these cases the therapy had resulted in dehydration and depletion of sodium chloride; since the introduction of the mercurial diuretics, such examples of dehydration as a result of "successful" treatment of heart failure are, it has seemed to me, not rare.

The content of the cardiac psychoses is almost always depressive in nature The patient suffers from delusions of persecution, he thinks his relatives are deserting him, the doctors and nurses are against him, and the orderly will not bring the bed-pan. He refuses food and medication Terrifying hallucinations cause him to scream out in terror. Periods of muttering delirium alternate with relative clarity. At times, he is somnolent, on other occasions wildly excited and maniacal Restraint is required, and the patient cannot be kept in the general ward; I have several times known suicide. If the delirium continues, the manifestations of heart failure are aggravated, the patient sinks into coma, and the scene is closed. That even severe psychoses of this type may be survived, though very exceptionally, was mentioned above

Somnolence in Chronic Anoxemia —A peculiar mental state occurs in some chronically cyanotic patients with right heart failure secondary to pulmonary disease, notably in the rare cases of pulmonary endarteritis ("black cardiacs," page 544), though I have seen it several times in the emphysema heart. These patients may lie in a somnolent or stuporous state for weeks at a time, being awakened with more or less difficulty The somnolence is evidently a result of anoxemia, for it may be alleviated in the oxygen tent.

PSYCHONEUROTIC SYMPTOMS AND HEART FAILURE

Consciousness of disease of the heart, be it real or fancied, terrorizes many people. From childhood on, they have thought of the heart as the mainspring of life and disease of the organ as inevitably fatal (some of the ancients did not admit the possibility of disease of the heart, regarding it as incompatible with life). Especially disquieting is the universal knowledge that heart disease may cause sudden death while the subject is feeling in perfect health

It is therefore not surprising that patients with organic heart disease, not to speak of the *cardiaques imaginaires*, often suffer from symptoms of psychoneurotic origin These symptoms born of the mind may be commingled with complaints of organic origin, and often it is a wise physician who can separate the two in a patient with actual cardiac lesions The difficulty is due to the fact that these "functional" complaints may include palpitation, shortness of breath, precordial pain and hyperesthesia, constriction of the neck and chest, in other words, the very complaints that could emanate from the structural changes in the heart or coronary arteries that are present Often, the separation of the organic and psychoneurotic elements in the clinical picture can be accomplished only after the physician has studied the patient for some time and has acquired an understanding of his personality No greater harm can be done many patients than by treating all their complaints as though they were of organic origin, digitalis does not heal the mind On the other hand, it may be tragic not only to the patient but also to the physician, to pass off complaints in too facile fashion as psychoneurotic in origin, many coronary thromboses have followed in the wake of the verdict that the complaints are due to nervousness

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CHAPTER XVIII

COMPENSATION OF THE HEART

SUCH pathological conditions as stenosis or insufficiency of a valve, functional impairment of the myocardium, or increased peripheral resistance, tend of themselves to diminish the volume of circulation. However, it is primarily the metabolic activity that determines the minute volume For this reason, one would anticipate, *a priori*, that the organism has at its disposal mechanisms which can be brought into play to counteract such impediments to the circulation as those mentioned, and thereby meet the circulatory needs of the metabolism of the moment. The actual existence of such *compensatory mechanisms*—the term compensation was introduced into circulatory pathology by Traube[69] in connection with cardiac hypertrophy—is immediately indicated by banal facts of clinical observation. Thus, it is commonplace to encounter a boy with aortic insufficiency who is able to participate in athletics without feeling any handicap, or a man with high blood pressure who has no difficulty in working as a laborer

The process of circulatory compensation is accomplished in three general ways.

1. Through mechanisms tending to maintain the minute volume of circulation despite the valvular defect or other handicap These involve not only increased work on the part of one or more chambers of the heart but often, in addition, coordinated adaptations of the vessels

2. Through vasomotor mechanisms tending to deviate a higher proportion of the decreased cardiac output to the active organs.

3. Through more efficient utilization of such volume of circulation as can be maintained Examples are the more complete reduction of hemoglobin in the capillaries (greater arteriovenous oxygen difference) as a result of the slowing of blood flow and the increased oxygen-carrying capacity of the blood due to the polycythemia that develops in certain congenital and other forms of circulatory impairment

The rôle of the heart in circulatory compensation will be considered first The cardiac compensatory mechanisms are three: acceleration of beat, dilatation, and hypertrophy. They are considered in this order because the first two can be brought into play immediately, while hypertrophy becomes significant only after a considerable period of strain.

ACCELERATION OF THE HEART*

Acceleration of beat is one of the means by which the output of the heart is augmented In health, it is exemplified by the remarkably prompt increase in rate that accompanies exercise, in fact, Buchanan[11] found that the first diastole after the start of exercise is already shortened When cardiac insufficiency is present, this is *manifested, as a rule, by a given amount of exercise involving greater* acceleration than when the heart is functionally competent With severe heart failure, tachycardia is necessary for maintaining even the basal circulation during sleep (Boas and Goldschmidt[10]) And when in disease the heart is called upon to keep up an abnormally great blood flow, the rate may be quickened even though the heart is functionally unimpaired, such is often the case in anemia and Graves' disease

However, by no means every tachycardia is to be regarded as forming part of a regulatory mechanism This is, of course, not true of auricular fibrillation, paroxysmal tachycardia, and other heterotopic accelerations, and of the rapid heart action that is so commonly a manifestation of psychoneuroses Often, indeed, the heterotopic tachycardias diminish cardiac output and precipitate heart failure in cases in which it was previously absent The present section will not be concerned with these forms of rapid heart beat, but will be confined to a discussion of tachycardia as a compensatory mechanism and what little is known of the means through which it is called forth

Relation of Output to Rate of Heart.—The influence of acceleration in beat on the output of the heart varies greatly at different rates This is due primarily, as was emphasized by Henderson,[30] to the fact that the velocity of filling of the ventricles is not uniform throughout diastole From the point of view of the rate of filling, ventricular diastole may be divided into three periods

1. Early diastole constitutes a period of rapid filling, for at this time the functionally competent ventricle contains only the small residuum remaining after the previous systole and its walls are relaxing, *in consequence, the inflow from the auricle and veins* meets with but minimal resistance

2. As a result of the rapid filling of early diastole, the intraventricular pressure is elevated and approaches the venous pressure, so that filling becomes very slow. This is the period that Henderson termed *diastasis*.

* Most of our information concerning the heart rate has been derived from brief individual observations Boas[9] has devised an ingenious instrument, the cardiotachometer, with which the heart rate can be recorded over long periods and while the patient is exercising or sleeping For numerous observations made with the cardiotachometer, the reader is referred to the monograph of Boas and Goldschmidt[10]

3. Finally, ventricular filling is suddenly accelerated and completed by auricular systole The quota contributed to ventricular filling by auricular systole is discussed on page 351.

The consequences of this unequal velocity of ventricular filling are as follows: When the heart rate is slow, changes in rate are almost entirely at the expense of the period of diastasis; the alterations in the duration of the early period of rapid filling, as well as of auricular and ventricular systole, seem to be comparatively insignificant Since ventricular filling during diastasis is minimal, the output of the heart up to a rate of about 80 beats per minute is very closely proportional to the rate. At higher rates, the early period of rapid ventricular filling is encroached upon, so that the output of the heart no longer increases *pari passu* with the rate but falls more and more behind it the faster the rate. Finally, further increase in rate so diminishes the period of rapid ventricular filling that the output decreases Wenckebach[73] further points out that at very rapid rates auricular systole starts before the termination of the preceding ventricular systole, which also tends to diminish cardiac output

One factor that militates somewhat against this diminution in output at very rapid rates is the shortening of systole found by Wiggers and Katz[74] in tachycardia due to sympathetic stimulation, and which has also been observed by Katz and Feil[19] in clinical auricular fibrillation This shortening of systole allows more time for ventricular filling. Katz and Feil believe the abbreviation of ventricular systole in auricular fibrillation results from the decrease in initial intraventricular tension due to the absence of auricular systole. The shortening of ventricular systole at very rapid rates allows more time for ventricular filling and thus tends to maintain the output. On the other hand, the decreased ventricular filling and initial intraventricular tension due to the loss of the auricular quota of blood in auricular fibrillation works against increased output from the more rapid rate.

The *height of the venous pressure* has a very important influence on the relation of heart rate to output. The higher the venous pressure the more rapidly the heart fills. The result is that at high venous pressures abbreviation of diastole by tachycardia is of less significance for the output of the heart than at lower venous tensions. Tachycardia and venous engorgement thus act synergistically in heart failure, for the shortening of diastole due to the tachycardia is to a certain extent atoned for by the rapid filling produced by the increased venous pressure. Quite probably, it is the simultaneous elevation of venous pressure that enables the heart to maintain the high arterial tension observed in exceptional episodes of paroxysmal tachycardia. On the other hand, the low venous pressure in peripheral circulatory failure (shock) militates against

increase in cardiac output by the tachycardia that is generally present.

While acceleration in rate of the heart may thus fulfill a very important compensatory function, it would seem that it diminishes the mechanical efficiency of the heart This is indicated by the findings of Starling and Visscher[64] on the heart-lung preparation of the dog. Their observations of the oxygen consumption at different rates showed that the heart performs a given amount of work in a unit of time the more economically the slower the rate. This decreased mechanical efficiency at high rates may be concerned in the pathogenesis of cardiac failure in paroxysmal tachycardia and other states of protracted acceleration.

Mechanism of Compensatory Tachycardia in Heart Failure.— Little is known of the means by which the failing heart is accelerated in the effort to maintain the volume of blood flow. Acceleration of beat is not an *intrinsic* adaptation of the heart to increased work, for in the heart-lung preparation accommodation to increased arterial resistance or greater venous return is accomplished without any change in the rate of the heart. It is not that the heart in such a preparation is unable to accelerate, for elevation in temperature is immediately followed by increase in rate. These observations on the isolated heart indicate that extrinsic mechanisms, be they nervous or chemical, are involved in the production of compensatory tachycardia in heart failure. Among the mechanisms that may be concerned are the Bainbridge and carotid sinus reflexes.

The Bainbridge Reflex.—Bainbridge[5] found that when he increased the venous return to the heart and with it the venous pressure by the injection of blood or salt solution, the heart was accelerated. He proved that the quickening of the heart beat is reflex in nature, for it does not appear after section of the vagus and accelerator nerves. His experiments showed that the acceleration of the heart is chiefly due to diminution in vagus tone but partly also to increased accelerator tone. Bainbridge believed that the reflex is initiated by impulses arising within the heart, the adequate stimulus of which is a rise in venous pressure. This view that the mechanical stimulus arising from increased venous pressure reflexly accelerates the heart was supported by experiments of Sassa and Miyasaki[60] They found that the distention of either auricle or of the inferior vena cava close to the heart with a balloon reflexly accelerates the heart. On the other hand, De Graff and Sands[20] observed an increase in heart rate following saline infusion in only about 50 per cent of their animals. Their other experimental results also did not support the view that the acceleration of the heart after saline infusion is due to a vagal reflex from the distended veins and right auricle. However, in their experiments with the innervated heart-lung

preparation, Anrep and Segall[9] confirmed Bainbridge's finding that increased venous return reflexly accelerates the rate, and were able to show that the afferent path of the reflex lies exclusively in the vagus. But Anrep and Segall often observed the Bainbridge reflex with only a minimal or even no rise in venous pressure. They "therefore think that the receptor part of the reflex arc should be still left open and it is premature to regard the venous pressure as being responsible for the reflex."

It would be very tempting to invoke the Bainbridge reflex as the cause of compensatory tachycardia, for in every instance of cardiac failure the tension in either the left auricle and pulmonary veins or the right auricle and vena cava is increased. And when the heart failure is compensated by hypertrophy so that the tension in the auricles and veins returns to normal, the tachycardia also disappears. It would, indeed, seem very plausible that the same mechanism which accelerates the heart in the above-mentioned experiments with increased venous return also functions in human heart failure. But in view of the uncertainty as to the nature of the Bainbridge reflex, its rôle in human tachycardia must be left open.

The Carotid Sinus and Aortic Reflexes.—One of the most important means for the regulation of the heart rate and blood pressure consists in a reflex mechanism maintained in tonic activity by the mechanical stimulus of the blood pressure. It has long been known that increase in aortic pressure slows the heart and lowers the blood pressure through mechanical stimulation of receptors situated in the arch of the aorta. The work of Daly and Verney[16] indicates that this reflex is initiated not only by rise of pressure in the aorta but also within the heart itself. Further, Hering[32] has found that a similar depressor reflex takes its origin in the ampulla-like dilatation (carotid sinus) situated at the bifurcation of the common carotid artery. The latter reflex is known as the carotid sinus reflex and its adequate stimulus is the blood pressure within the carotid sinsus; the afferent arc runs largely within the glossopharyngeal nerve.

These reflexes from the heart, aorta, and carotid sinus constitute a reflex autoregulation of the blood pressure. They are tonically active, for if the afferent fibers of the reflex arc are interrupted, the blood pressure rises and the heart accelerates. On the other hand, if the blood pressure is elevated by any means, the mechanical stimulation of the receptors of this mechanism tends to lower the blood pressure by reflex vasoconstriction and slowing of the heart. In fact, these reflexes are the mechanism of what has long been known as Marey's law, *i. e.*, that the blood pressure and heart rate vary inversely. For details as to the reflex autoregulation of the blood pressure and heart rate, the reader is referred to the monographs of Hering,[32] Heymans,[35] Koch,[43] and Weiss and Baker.[72]

A priori, it would seem probable that these reflexes play an important part in compensating for the dynamic consequences of circulatory failure and especially in bringing about compensatory tachycardia. Thus, in peripheral circulatory failure (shock) the low blood pressure is generally accompanied by a rapid heart rate. The latter cannot be due to any form of Bainbridge reflex (see above) because the pressure in the great veins is abnormally low. It would therefore seem very likely that the heart is accelerated in such cases through the diminished tonic activity of the carotid sinus and aortic reflexes due to the lowered blood pressure. In heart failure, in which diminished cardiac output and elevated venous pressure are generally combined, it may well be that both the Bainbridge and the carotid sinus and aortic reflexes participate in producing tachycardia. But these are as yet merely suppositions without positive evidence to support them

It may be remarked that Wenckebach's observation that "vagus pressure" more often produces a marked slowing of the heart when the myocardium is damaged than in health indicates that the carotid sinus reflex is very active in these patients For a long-known slowing following what was considered vagus pressure is now known to be a manifestation of the carotid sinus reflex

DILATATION OF THE HEART

Cardiac insufficiency is accompanied by dilatation of one or more chambers of the heart. Most often the enlargement is demonstrable by either physical or radioscopic examination, but even if this is not feasible, the postmortem examination of an individual who has succumbed after a period of more than momentary heart failure *other than that due to compression of the heart reveals the dilatation.*

Pathological Anatomy.—The only characteristic of a dilated chamber of the heart is the increased capacity of its cavity When this is comparatively slight, it may be masked by postmortem contraction—which generally involves the heart between one and two hours after death, although there is great variation depending on the nature of the disease and activity of the individual ante mortem—but the dilatation is again evident after the myocardium relaxes While dilatation as such tends to thin the wall of the affected chamber, *the latter may nevertheless be decidedly thicker than normal* because of concomitant hypertrophy, which is almost always present when dilatation has existed for more than a few weeks. In other instances, the thinning of the walls of the heart is very marked, this is most conspicuous in the auricles, which may be almost paper thin, or where an aneurysm has formed in consequence of fibrous replacement of infarcted myocardium. The extent of dilatation

may be enormous; when both sides of the heart are thus affected, the organ may extend from the left axilla almost to the right. The highest degree of dilatation is seen in the auricles. In rare instances of mitral stenosis, the capacity of the left auricle exceeds a liter. With the thinning of the walls of the dilated chamber goes an attenuation and elongation of the papillary muscles and chordæ tendinæ as well as flattening of the trabeculæ of the ventricles and the musculæ pectinatæ of the auricular appendages; in extreme instances the latter may be hardly discernible. An important accompaniment of some instances of well-marked cardiac dilatation is enlargement of the auriculo-ventricular orifices, usually much more marked in the tricuspid than in the mitral valve. While the arterial rings may also be dilated, this is usually much more closely correlated with the state of the aorta and pulmonary artery. With high-grade dilatation and hypertrophy of the left ventricle, the septum protrudes far into the right ventricle, so that the cavity of the latter appears crescentic in transverse section and its capacity is greatly diminished (page 447). Depending on the direction of the enlargement, the dilated heart may compress any of the surrounding structures—lungs, diaphragm, esophagus, bronchi, etc. The changes in the external form of the dilated heart will be considered in conjunction with the clinical findings (page 362).

A fact of great interest in regard to the interpretation of dilatation is that it does not from the start involve the entire ventricle but evolves in characteristic fashion. Knowledge of the distribution of dilatation is largely due to the careful measurements of the various internal and external dimensions of the heart carried out by Kirch[41] His studies were especially concerned with the relations of the inflow and outflow tracts of the ventricles. The inflow tract of the left ventricle extends from the mitral orifice to the apex, that of the right ventricle from the tricuspid valve to the apex. The corresponding outflow tracts extend from the apex of each ventricle to the aortic and pulmonary orifices respectively. Studying the left ventricle in hypertension and aortic valvular disease and the right ventricle in conditions with increased pulmonary resistance (mitral disease, emphysema), Kirch found that *dilatation of a ventricle in these conditions always begins in the outflow tract*, which is both elongated and broadened. Moreover, he found that dilatation starts in the terminal portion of the outflow tract, under the aortic ring in the left ventricle and in the pulmonary conus in the right. The dilatation then progresses against the direction of the blood stream down the outflow tract to the apex. Only subsequently is the inflow tract involved, again in a direction contrary to that of blood flow, so that the dilatation finally reaches the auriculo-ventricular ring with the production of relative incompetence. While Kirch thus found many instances in which the outflow tract

(of the left ventricle in hypertension and aortic disease, and of the right ventricle in mitral disease and emphysema) was dilated while the inflow tract was normal, he did not observe the reverse in over ten years of investigation.

In mitral valvular disease with pronounced regurgitation, the dilatation of the left ventricle may be especially marked immediately under the mitral valve, so that the chamber tends toward a spherical shape. The dilatation resulting from myocarditis or coronary arteriosclerosis seems to involve all parts of the ventricle in question quite uniformly.

Another important observation made by Kirch concerns the anatomical difference between tonogenous and myogenous dilatation. (*For definition of these terms see page 304*) *He found that in* tonogenous dilatation the principal change is *elongation* of the outflow and then of the inflow tract of the ventricle involved, while in myogenous dilatation broadening predominates over elongation. He observed elongation of over 20 per cent above the normal with no more than minimal broadening in the apical region Since tonogenous dilatation is generally the basis on which the heart hypertrophies in, for example, arterial hypertension, these observations of Kirch furnish the anatomical basis for the well-known *fact that in relatively well-compensated hypertension of many* years' standing, fluoroscopic examination generally reveals little or no increase in the transverse diameter of the heart but only an often marked elongation of the left ventricle far down into the shadow of the diaphragm. But when failure develops in such a case as a result of coronary arteriosclerosis, the resulting myogenous dilatation is marked by broadening of the organ. Kirch also believes that the fact that tonogenous dilatation is predominantly longitudinal is one of the reasons why roentgenographic examination *of the heart immediately after exercise does not reveal the* enlargement that would theoretically be expected (page 300). The independent behavior of the outflow and inflow tracts as regards dilatation and hypertrophy (page 314) is evidently an expression of functional differences between the two portions of the ventricle, the nature of which remains to be elucidated

The histological changes in the dilated heart will be considered in connection with the causes of heart failure (page 322).

The Compensatory Nature of Cardiac Dilatation.—To the clinicians of a century ago, dilatation of the heart was solely a passive process, for which reason they termed it "passive aneurysm" in contradistinction to hypertrophy or "active aneurysm." They regarded dilatation as analogous to the stretching of old rubber, solely a manifestation of impaired contractility, and in itself purely deleterious to the function of the myocardium. The first to oppose this view seems to have been Rosenbach,[58] who pointed out, largely

on speculative and teleological grounds, that cardiac dilatation may at times be a useful, compensatory process serving to increase the capacity for work of the dilated chamber. For this reason, he spoke of "hyperdiastole."

Adequate basis for this conception has since been furnished by studies of physiologists on the dynamics of the heart The fundamental experiments are those of Frank[25] on the frog's heart and especially of Starling[63] and his pupils on Starling's mammalian heart-lung preparation * Since the resulting knowledge of the dynamics of heart muscle forms the cornerstone of present conceptions of the pathological physiology of the heart, it will be briefly discussed here

Experimental Investigation of Cardiac Dilatation.—These studies have shed bright light on the interpretation of cardiac dilatation For it was found that *when either heightened arterial resistance or greater venous inflow increases the work of the heart accommodation to the greater load involves dilatation of the heart.* The steps in the accommodative process were found by Starling to be as follows:

When the resistance in the aorta is increased, the heart fails to empty during the first beats as completely as before. The result is that the residual blood in the left ventricle at the end of systole rises progressively with each of these beats. Inasmuch as the venous inflow during diastole remains constant, there is corresponding increase in the volume of the ventricle at the end of diastole, *i e.*, of what may be termed the presystolic volume. However, as the presystolic volume mounts with successive beats, the output also rises until equilibrium is attained by output equalling inflow.† The circulation has thus been adjusted to the new condition of increased resistance in the aorta But this readjustment has been attained only at the expense of the following new conditions:

1. Both the presystolic and the systolic volumes of the heart are greater. In other words, although the output of the heart is the same as at the lower resistance, it is effected from a higher level of dilatation.

* In the heart-lung preparation of Starling, the heart and lungs of a dog or cat are completely severed from the rest of the body and a circulation maintained through them by the heart Such a heart may beat for many hours and, according to Starling, be regarded as practically normal for three or four hours Both the venous return to the heart and the arterial resistance can be varied at will Among the measurements that can be carried out are those of the volume and output of the heart, the pressure in the chambers, and the coronary blood flow The gaseous metabolism of the heart can be studied by means of the respiratory gases

† As regards the form of the more powerful systole, Patterson, Piper and Starling[63] observed it to be more prolonged On the other hand, Wiggers and Katz[74] found that when the resistance is augmented by compression of the aorta, systole is abbreviated but the ejection gradient is steeper, so that the same volume of blood is discharged in a shorter time If the heart is insufficient, they found that while systole is likewise shortened the ejection gradient does not become steeper, so that the output is lessened

2. The pressure in the pulmonary veins and that in the left auricle is increased. This results from the venous return remaining constant in the face of a greater volume of residual blood in the left ventricle at the end of diastole so that the ventricle is more distended during diastole and the diastolic intraventricular pressure rises, which results in a rise in pressure in the left auricle and pulmonary veins. It will be pointed out later that the elevation of pressure in the pulmonary veins is probably of primary importance in causing dyspnea in left heart failure.

3. Starling found that as the arterial resistance is increased, a greater proportion of the output of the left ventricle passes through the coronary circulation. This is, of course, a very useful adaptation, for the heart is performing more work and therefore needs more blood. It is worthy of consideration whether the increased coronary flow accompanying heightened arterial resistance does not play a significant part, through producing greater wear and tear, in the genesis of coronary arteriosclerosis in hypertension.

A similar adaptation was found by Starling when the arterial resistance was kept constant while the venous return to the heart was increased. Here, also, the output of the first few beats of the heart falls progressively behind the inflow so that the presystolic volume of the heart increases. But as the volume of the heart at the end of diastole increases with each beat, the output also rises until equilibrium with the increased venous return is attained. Starling and his associates found that the volume of the heart at the end of systole was greater than with a lower venous return. However, although they made no actual observations of this type, Patterson, Piper and Starling conceive it theoretically possible that a heart of very great physiological efficiency would be able to discharge all the surplus blood it received and thus maintain the larger stroke volume with only diastolic but no systolic dilatation. According to Wiggers and Katz,[74] the increased output following augmentation of venous return is accomplished by both greater velocity of ejection and prolongation of systole.

Of especial importance is the fact, demonstrated by these and other experiments, that *the isolated heart accommodates itself to either increased arterial resistance or greater venous return solely by increasing the energy of the individual contractions and not by increasing the rate.* In Starling's experiments, the latter remained constant with the most varied arterial resistances and venous returns. But the rate was immediately altered by change in temperature. These findings indicate that the tachycardia of heart failure is an extrinsic adaptation, probably dependent on the nervous control of the heart.

It may be remarked that these experiments on the heart-lung preparation showing that the increase in cardiac output following greater venous return to the heart is accomplished through the

intermediacy of dilatation of the heart have been confirmed on the intact animal by Wiggers and Katz and Meek and Eyster.[50]

Starling's Law of the Heart.—On the basis of these observations that the accommodation of the heart to either increased resistance or greater venous return is associated with dilatation, Starling enunciated his *law of the heart*, so fundamental for the clinical study of cardiac failure. "Within physiological limits the larger the volume of the heart, the greater are the energy of its contraction and the amount of chemical change at each contraction." Since dilatation of the heart means that the constituent muscle fibers are elongated, the behavior of the cardiac muscle in this respect is the same as that of voluntary muscle. For it has long been known that the energy of contraction of skeletal muscle increases with its length at the beginning of the twitch.

Mechanism of Compensation by Dilatation.—The nature of the connection between the increased initial length of the muscle fiber and the accompanying greater energy of contraction is not clear. The reason for this difficulty is largely that the increase in initial length is generally accompanied by increase in tension. Starling believed it is the greater length as such that results in more energy being liberated in the following systole. He based this opinion on observations in which the increased diastolic volume of the heart was accompanied by but minimal *increment in tension*, but was nevertheless followed by a much more powerful systole. Starling's conception was that muscular contraction is largely dependent on surface energy developed along longitudinally disposed surfaces, which are increased when the muscle is elongated. Straub[65] does not accept Starling's evidence that it is the increase in presystolic length of the muscle fibers and not their presystolic tension that determines the more powerful systole. On the contrary, he finds that in the case of the mammalian heart under the influence of vagal stimulation, the initial volume may be high although both initial tension and systolic accomplishment are low. Wiggers and Katz were unable to dissociate changes in presystolic volume from those in tension Gesell[26] believes that both increase in initial length and in tension of the fibers are concerned *in augmenting the* strength of ventricular contraction.

Whatever may be the outcome of this controversy, for the clinician these experimental studies have furnished the significant demonstration that cardiac dilatation is one of the means by which the heart adapts itself to increased work.

Metabolism of the Dilated Heart.—When the heart masters greater venous return or arterial resistance by means of diastolic dilatation, it performs more mechanical work. In accord with this, Evans and Matsuoka[22] found that when the arterial resistance or the venous inflow is increased, there is a rise in the oxygen con-

sumption and carbon dioxide production of the heart In a subsequent investigation, Starling and Visscher[64] showed that the oxygen consumption of the heart (in the heart-lung preparation of the dog) varied in the same sense as its diastolic volume and the initial length of the muscle fibers. They also showed that as the heart tires, its mechanical efficiency decreases, *i. e*, dilatation and oxygen consumption increase although the work accomplished becomes less.

The increased metabolism of the heart with progressive dilatation is probably often of significance for the pathogenesis of cardiac failure. Thus, if the coronaries are sclerotic, the blood supply may be inadequate for the greater metabolism accompanying dilatation due to high blood pressure or a valvular defect

Optimal Dilatation and Pericardial Restraint.—Just as the energy of contraction of skeletal muscle increases with initial elongation only up to a certain maximum, there is also an optimal dilatation for the heart. If the venous pressure or arterial resistance continues to increase so that the dilatation exceeds this optimum, the energy of systolic contractions decreases, the residual blood in the ventricle at the end of systole mounts rapidly with corresponding drop in output, and the heart fails. In their experiments, Wiggers and Katz found that when the venous pressure exceeded a critical level of between 250 and 310 mm of saline, the systolic discharge decreased. What determines the degree of dilatation above which the output of the heart decreases is not known. One factor probably is the greater tension on the muscle fibers. For if the pressure within the chamber remains constant, the tension on each individual fiber increases with the radius. The maximum tension which the muscle fibers can withstand without giving way is presumably a function of their physiological fitness But this is only another way of saying that they have failed and adds nothing to our comprehension of the mechanism.

Such sudden dilatation of the heart beyond the optimum, which would be followed by quick failure, is largely prevented by the pericardium. In health, the heart does not fill the pericardium, so that room is available for some dilatation While the findings in pericardial effusion and in enlargement of the heart show that the pericardium can dilate enormously as a result of gradual pressure, it is practically inextensible to sudden stretching and thus will prevent very great immediate dilatation The restraint of dilatation by the pericardium is well brought out in the experiments of Van Liere[71] and his associates, who showed that the pericardium prevents excessive dilatation following vagal stimulation and that the cardiac dilatation due to severe anoxemia is greater in animals with the pericardium removed Working with the heart-lung preparation, Kuno[46] found that if the pericardium is removed any increase in

the work of the heart is dangerous to the organ, for hemorrhages into the myocardium or valvular incompetence may develop. On the other hand, he observed that with the pericardium intact the heart requires a higher venous pressure to perform a given amount of work than when the pericardium is opened; this is presumably because the heart dilates more readily in the absence of pericardial restraint. Gibbon and Churchill[27] also found that removal of a pericardium which interferes with the dilatation of a heart performing increased work "materially lessens the degree of cardiac decompensation." These observations leave no doubt that the pericardium serves to prevent excessive dilatation. Attempts have been made by Felix[24] and others to facilitate compensatory dilatation by opening the pericardium.

Varieties of Dilatation.—Moritz,[53] Hering,[31] and others have endeavored to differentiate pathogenetically distinct varieties of dilatation The main types recognized have been:

1 A purely compensatory dilatation of the healthy heart muscle in order to meet a greater load. This is the so-called physiological or active dilatation, termed by Moritz *tonogenic dilatation* (*i. e*, due to increased tension) The conception has been that in this variety the heart is dilated only in diastole while the systolic volume is normal However, the experiments on the heart-lung preparation cited above indicate that the residual blood in the ventricle at the end of systole is increased even in a healthy heart when the arterial resistance is elevated.

2. Dilatation due to impaired contractility of the damaged myocardium (pathological or passive dilatation, *myogenic dilatation* of Moritz)

3 Dilatation due to diminished diastolic tone of the heart Hering conceives that this may result from either increased vagus or decreased accelerator tone This form is hypothetical as far as human pathology is concerned. (See next section.)

In clinical work, it is often impossible to differentiate the rôle played by myogenic and tonogenic factors in producing dilatation, *e g.*, in valvular lesions or hypertension with associated myocardial changes. There are, however, dilatations which can be classified as purely myogenic or tonogenic. Examples of myogenic dilatation are encountered in, for example, arteriosclerotic myomalacia without hypertension, post-diphtheritic heart disease, and rheumatic myocarditis with little valvular defect. Tonogenic dilatation occurs in nephritic or essential hypertension in the young, although even here, despite the fact that the coronary arteries are widely patent and histological examination reveals no lesions of the heart muscle, the question may be raised whether superadded myogenic factors are not also concerned.

From the point of view of the compensatory nature of the process,

it does not seem that a distinction can be drawn between myogenic and tonogenic dilatation. For even when the dilatation results from damage to the heart muscle and not from increased load, the greater volume of the heart is accompanied by augmentation in the energy of systolic discharge. Evidence to this effect is afforded by the experiments with the heart-lung preparation of Socin,[61] who injured the heart with chloroform, and those of Sulzer,[67] who used alcohol for the same purpose. These investigations revealed that the dynamics of the hypodynamic heart is *qualitatively* identical with that of the healthy organ Just as is true of the latter, increased filling and greater arterial resistance are met by dilatation, as a result of which systolic energy is increased and the greater load mastered. But Socin found that in order to meet a given load, it was necessary for the heart damaged by chloroform to undergo greater diastolic dilatation and accumulate a larger systolic residue than was needed by the healthy heart Furthermore, the damaged heart failed at a smaller load than did the healthy one In other words, *dilatation of the damaged heart fulfills the same function of increasing the energy of systolic contraction as does dilatation when the heart muscle is uninjured* Thus, it would seem that myogenic dilatation is to be viewed as essentially similar to the dilatation that the healthy heart undergoes in the face of an increased load; it is present because the injured heart muscle can meet the normal load only with a greater presystolic fiber length (or tension) than the undamaged cardiac muscle requires

The Question of Diminished Tone in Dilatation.—Loss of tone of the heart muscle has often been attributed a rôle in the production of dilatation To Mackenzie,[48] dilatation of the heart seems to have been practically synonymous with diminished tone When fluoroscopic examination reveals a dilated heart in which the differentiation of the individual segments of the borders is less clear than usual, which lies with a broad base on the diaphragm, and the amplitude of the pulsations is diminished, the tone of the heart is often considered to be low Even at the postmortem table, the flabbiness of the heart muscle often encountered in post-diphtheritic or other myocardial degenerations or inflammations is not uncommonly considered to indicate that the tone of the heart was low during life.

It seems, however, that these clinical interpretations are based on a loose conception of the nature of tone Tone is a fundamental property of both smooth and skeletal muscle, consisting in the maintenance of a sustained, most often relatively slight, degree of contraction In the case of the heart muscle, Meek[49] defines tone as "a condition of sustained diastolic contraction, by virtue of which the muscle fibers resist distention more than they would because of their mere physical properties" Such a diastolic tone

might obviously be of great significance for the regulation of cardiac activity And indeed the existence of cardiac tone in this sense was long ago established for the tortoise heart, where it seems to reside in a layer of smooth muscle most highly developed in the auricle but also present in the ventricle. There have been many attempts to demonstrate the presence of similar diastolic tone in the mammalian heart as manifested by altered ventricular dilatation for the same venous return, and especially to show that vagal stimulation diminishes the tone However, as the result of an excellent review of the subject, Meek comes to the conclusion that *there is as yet no adequate evidence of the existence of diastolic tone in the mammalian heart*, although the possibility cannot be considered as disproved. In their experiments on the heart-lung preparation, Patterson, Piper and Starling[63] found no evidence of the existence of diastolic tone as defined above They therefore propose that the word *tone* be used to designate the physiological fitness of the muscle fiber as measured by its efficiency in carrying on the circulation without elongating It seems to me that if thus defined, the property of tone is not differentiated from that of contractility and loses all meaning as an independent concept

In view of the uncertainity regarding the existence of diastolic tone—strictly defined as above—in the mammalian heart, the use of the concept in clinical medicine does not appear warranted. So far as is known, dilatation of the heart results from failure of the systolic accomplishment of the heart to equal the venous return. (For contrary views see Straub[65] and Hering.[31])

HYPERTROPHY OF THE HEART

Of the three adaptations of the heart to increased work—acceleration in rate, dilatation, and hypertrophy—the compensatory nature of the last-named seems the most obvious That hypertrophy results from increased work of the heart was appreciated by Corvisart,[15] who drew an analogy between "active aneurysm," as hypertrophy was then known, and the massive arm of the blacksmith. Subsequent work has only fortified this conception that *the mass of the myocardium is a function of the work it performs, with the limitation that the work must be considered in relation to the functional fitness of the myocardium.* The supporting evidence is derived from observations both in health and in disease.

Relations of Cardiac Work and Mass in Health.—The comparative anatomical studies of Bergmann[8] showed that among different species of mammals the ratio of the heart weight to that of the entire body tends to parallel the physical activity. The very active hare had the highest relative heart weight among the mammals he studied. Wild animals were found to have heavier hearts than

domesticated members of the species. Similarly, Herrmann[33] has recently found that the heart is relatively more massive in race horses and racing greyhounds than in others of the same species. Among birds, Parrot[55] observed the heaviest hearts in those which fly the most and the fastest and those which sing the most.

In humans, Mueller[54] long ago found that the heart weight tends to increase with the body weight. He also showed, however, that the absolute increase in the mass of the heart falls behind that of the body, so that the heavier the individual the less the ratio $\frac{\text{heart weight}}{\text{body weight}}$. Mueller's findings were later amended by Hirsch,[36] who demonstrated that the closer parallelism is between the heart weight and the general muscular development of the individual, fat but flabby individuals generally have comparatively light hearts. Such direct correlation of the mass of cardiac and skeletal muscle is, of course, what one would expect if the mass of the heart muscle is a function of the work it performs That hard-working men usually have relatively massive hearts is indicated by radiographic and especially necropsy experience, I have repeatedly seen a heart weight exceeding 450 grams in such individuals in the absence of hypertension or cardiac disease. The roentgenographic studies carried out by Herxheimer[34] on participants in the Olympic games revealed that athletes, especially those participating in endurance events, often have enlarged hearts. His orthodiagraphic measurements showed that the enlargement of the heart in trained participants in such exacting sports as rowing and marathon running is often decidedly greater than the hypertrophy of the skeletal musculature Roesler[66] also showed that in healthy athletes the heart may be slightly enlarged, and diminish in size after the cessation of training. Likewise, Tung[70] and his associates have found that 45 per cent of Chinese ricksha pullers, who perform very hard work, have enlargement of the heart sufficient to be demonstrable during life.

Experimentally, Kuelbs[44] showed that when the work of the heart is increased by exercise, it hypertrophies He studied two dogs of a litter on the same diet. One was kept quiet while the other was exercised vigorously through a period of months The weight of the heart of the exercised dog was much greater, not only in proportion to the body weight but also to that of the entire skeletal musculature. Further experiments have shown that after the termination of the period of exercise the heart decreases in weight. Kirch and Nuermberger[42] similarly produced hypertrophy of the heart in rats by very severe exercise, the hypertrophy was already present six days after the start of the training and disappeared after five or six months rest.

Most interesting quantitative experiments were carried out by

Chanutin and Ferris[14] and Chanutin and Barksdale.[13] They produced chronic hypertension in rats by partial nephrectomy and found a close direct correlation between the height of the blood pressure and the value of the ratio $\frac{\text{heart weight}}{\text{surface area}}$. Chanutin and his associates were further able to demonstrate a close parallelism between the elevation in blood pressure and the thickness of the fibers of the left ventricle The right ventricle exhibited no hypertrophy These experiments afford a beautiful illustration of variation of the thickness of the myocardial fibers as a function of the work they perform.

Cardiac Hypertrophy in Disease.—Increase in the mass of the heart disproportionate to the development of the skeletal musculature occurs under two general conditions:

1. When the work of a cardiac chamber is increased in an *absolute* sense. Examples are the hypertrophy occurring in hypertension of either circulation, valvular defects, some forms of adhesive mediastino-pericarditis, etc. The hypertrophy is confined strictly to the chambers which perform the increased work. It has been gratuitously assumed in the past that when a chamber of the heart hypertrophies because of increased work, there might also develop a "sympathetic" hypertrophy of another chamber on the basis of muscle fibers common to both chambers or because the blood supply to the second chamber was also increased, a pure hypothesis without tangible support. Such explanations have been advanced, for example, for the hypertrophy of the right ventricle that so often accompanies that of the left ventricle in hypertension. But it has long been established that such hypertrophy of the right ventricle occurs only after the left ventricle has become insufficient and the consequent rise in pressure in the pulmonary circuit increases the work of the right ventricle. The above-mentioned experiments of Chanutin and Barksdale showed conclusively that in hypertension without heart failure only the left ventricle is hypertrophied. In fact, the location of hypertrophy is even more selective than the involvement of the overworked ventricle; the work of Kirch shows that hypertrophy of the left ventricle in hypertension and aortic disease at first involves only the outflow tract (page 314). Moreover, not only does an increment in the work of a chamber result in hypertrophy of its muscle, but decreased work is followed by atrophy of the myocardium to less than its previous mass The outstanding example is the small left ventricle of some instances of mitral stenosis.

The findings in Graves' disease indicate that it is increase in *work per stroke* rather than increase in work per minute that leads to hypertrophy of the functionally unimpaired heart. Many young individuals with Graves' disease have a very high basal metabolism

and consequently a greatly increased cardiac output (page 561) for several years with no demonstrable enlargement of the heart, and at postmortem the latter may not be hypertrophied In these cases, it seems plausible that the increase in minute volume is accomplished wholly by acceleration in rate without increment in stroke volume. In other instances of Graves' disease, the heart does become hypertrophied, and here it is to be presumed that either the stroke volume is increased or there is functional impairment of the myocardium. In accord with this conception of the relation of cardiac hypertrophy in Graves' disease, measurements of the cardiac output indicate that in some instances increase in the latter is effected wholly or almost wholly by acceleration in rate, while in others the stroke volume is also notably increased (page 562).

2. Hypertrophy may develop when the functional capacity of the myocardium is impaired, even though the work it is called upon to perform is not elevated. Nevertheless, although the absolute work of the heart is not augmented, there is a *relative* increase in the sense that the actual work performed approaches more closely to the maximum of which the heart is capable. Hypertrophy of this nature is seen in some cases of rheumatic myocarditis with little endocardial or pericardial involvement The same occurs in other varieties of myocardial inflammation or degeneration, very large hearts are encountered in the rare cases of chronic myocarditis of obscure origin. And there are instances of arteriosclerotic heart disease with pronounced hypertrophy although there is neither hypertension nor valvular defect. I have known a number of such cases in which the history indicated that hypertension had not previously been present, and in which corroborative evidence was furnished at necropsy by the absence of renal arteriolosclerosis In a series from which hypertension, valvular disease and other causes of hypertrophy were eliminated, Davis and Blumgart[19] found that the weights of the heart with severe coronary arteriosclerosis showed a higher range of distribution than those without marked changes in the coronary arteries It is true, however, that by no means all cases of arteriosclerotic heart disease develop notable cardiac hypertrophy. Where the latter is absent, it is to be presumed that the myocardial changes of any considerable duration are so discrete as not to produce cardiac insufficiency, at least for the restricted life that such patients usually live in consequence of anginal symptoms and for the low arterial pressure so often present in those who have survived coronary thrombosis

Very often, of course, increase in cardiac work and myocardial damage are combined in producing hypertrophy. Such is the case in valvular defects with accompanying rheumatic myocarditis and in hypertension with coronary artery disease In the often marked hypertrophy and dilatation of untreated pernicious anemia, both

overwork in maintaining the increased minute volume and functional impairment of the myocardium are probably concerned. A similar combination is doubtless guilty in many cases in which dilatation and hypertrophy of the heart supervene in Graves' disease.

Mechanism of Cardiac Hypertrophy.—We know as little of the actual biological processes through which absolute or relative increase in work results in cardiac hypertrophy as we do of those through which the exercise of his occupation results in thickening of the blacksmith's arm. Quite probably, the processes are fundamentally the same in both instances. But from consideration of the conditions under which the heart hypertrophies, certain interesting and important points of view are opened up.

In the foregoing, it has been seen that a chamber of the heart hypertrophies:

1. In health, when as a result of physical exertion the work of the heart is increased Here, it is important to note that the work per stroke is increased, for several investigators (Bainbridge[6] and Christensen[15]) have shown that in vigorous exercise the minute volume is increased more than the rate so that the heart must put out more blood per stroke.

2. When the resistance to the expulsion of the blood is increased by valvular stenosis or hypertension.

3 When in addition to expelling the blood, the heart has to drag the chest wall with it during systole, as occurs in some cases of adhesive mediastino-pericarditis

4. When the volume of blood expelled per stroke is increased, as in valvular insufficiency, and some instances of Graves' disease and anemia.

5 When the functional capacity of the myocardium is decreased for a considerable time as a result of inflammatory or degenerative lesions or impairment of blood supply.

Common to each of these five circumstances is that the heart calls upon its *reserve energy*. Under circumstances of rest the functionally efficient heart does not bring into play all the energy of which it is capable. The difference between the energy utilized at rest and the maximum energy which the heart is capable of evolving constitutes the reserve energy. But we have seen above that, in addition to acceleration in rate, the mechanism through which the heart brings its reserve energy into play involves increase in the initial length of the muscle fiber as it starts to contract, *i. e.*, dilatation In other words· *dilatation is the basis on which hypertrophy arises.*

Certain other evidence supports the view that hypertrophy evolves from antecedent dilatation Rosenbach[58] showed long ago that when aortic insufficiency is produced experimentally, the first

consequence is dilatation of the left ventricle. But after a period of time hypertrophy is added to the dilatation. This observation has been confirmed by Eyster, Meek and Hodges,[23] and others. A similar sequence of events is very clear in acute glomerulonephritis with hypertension. Occasionally, the sudden rise in blood pressure, perhaps with damage to the myocardium, results in acute left ventricular failure with death from pulmonary edema in the first weeks of the disease. In such cases, the left ventricle is found markedly dilated but the weight of the heart does not reveal definite hypertrophy. But in other cases which succumb after hypertension of a few months' duration, the left ventricular hypertrophy is very evident. The cardiac findings in Graves' disease (page 562) are also in excellent accord with the conception that hypertrophy evolves from dilatation. Finally, the intimate association of hypertrophy with antecedent dilatation is supported by the studies of Kirch (page 299), who found that both dilatation and hypertrophy in hypertension are initiated in the outflow tract of the left ventricle and both progress similarly to involve the inflow tract.

While it thus appears highly probable that dilatation always precedes hypertrophy, there are hypertrophic hearts in which dilatation cannot be demonstrated at postmortem. These are instances of what has long been known as *concentric hypertrophy.** They are more accurately termed hypertrophy without dilatation, for the seeming diminution in the capacity of the chamber is only simulated by postmortem contraction of the thickened wall. In such cases, it seems highly probable that the hypertrophy has supervened at a relatively slight degree of dilatation which, even if it persisted to the time of death, would be difficult of demonstration in the cadaver. Moreover, it is also likely that as hypertrophy becomes functionally more adequate, the antecedent dilatation may diminish, I have made several observations in acute glomerulonephritis and aortic regurgitation that would seem to accord with this view.

Functional Value of Cardiac Hypertrophy.—No direct, quantitative data seem to be available concerning the force of contraction of the hypertrophied heart. An approach to this important problem

* In an interesting investigation, Rytand and Dock[19] produced a form of cardiac hypertrophy which they regard as concentric. Rytand and Dock define concentric hypertrophy of the ventricle as "an increase in the volume and weight of its myocardial fibers caused by an increase in the width of the fibers, it is associated with a relatively small ventricular cavity, no significant increase in capacity per unit of body surface area and a shortening of the total length of the fibers." They found that when hypertension is produced in the rat by partial nephrectomy, the hypertrophy of the left ventricle is due entirely to increase in width of the myocardial fibers, while their length is diminished. The capacity of the left ventricle was little changed, increasing from a mean of 71 c mm per 100 sq cm of body surface in the controls to 75 c mm in the hypertensive animals. But since the general conception of concentric hypertrophy includes an actual diminution in the capacity of the chamber, misunderstanding may be avoided by not using the term concentric hypertrophy even for such hypertrophy as that produced by Rytand and Dock.

was made long ago by Hasenfeld and Romberg[29] on animals in which they had produced aortic regurgitation. The aorta was compressed and the maximum pressure which the heart was able to maintain measured. They found that a higher pressure was attained after the animal had developed cardiac hypertrophy than shortly after the production of the valvular defect, which would indicate that hypertrophy had rendered the heart more powerful. Despite this paucity of direct evidence, analogy indicates very strongly that hypertrophy augments the force with which a cardiac chamber contracts. For we know that when a skeletal muscle increases in cross-section it becomes more powerful, and there is every reason to believe that hypertrophy of the heart muscle is an analogous process. In the light of current conceptions of the regulation of the force of cardiac contraction (page 300), this may be expressed as follows: *Hypertrophy of a chamber of the heart results in a more powerful systole from a given diastolic filling than was the case before the hypertrophy developed.* Hypertrophy thus enables an overtaxed chamber of the heart to meet the demands on it with less dilatation and a lower diastolic tension within the chamber than without the hypertrophy.

In the foregoing, we have seen that hypertrophy appears to be always a sequel of dilatation. *Hypertrophy is, in a certain sense, an adaptation to the altered dynamic conditions resulting from dilatation.* This may be elucidated by the following considerations: Inasmuch as the volume of a sphere is proportional to the cube of the radius, as a sphere increases in size equal increments in volume correspond to smaller and smaller increases in radius. In other words, the larger a cardiac chamber the less its radius must be diminished to expel the same volume of blood. Consequently, the fibers of the dilated heart contract a shorter distance in maintaining the same stroke volume than do those of the normal organ. But the strength of contraction must be correspondingly greater because the tension on the muscle fibers increases in direct proportion to the radius.* *Dilatation thus leads to the necessity for a shorter but more powerful contraction of the muscle fibers, and hypertrophy would seem to be the adaptation to these altered conditions.* Of course, such a line of thought merely considers the wherefore and not the how of the process by which hypertrophy develops in the dilated heart. In accord with the conception is the above-mentioned finding of Rytand and Dock that the fibers of the hypertrophied myocardium are shorter than normal.

* This follows from an equation derived by Helmholtz: $T = P \times R/2$, where T is the tangential tension in the wall of a sphere, P is the pressure within the sphere, and R is the radius of the sphere. It is seen that if the pressure remains constant the tension in the wall varies directly with the radius. While, of course, a cardiac chamber is not a perfect sphere, the approximation is close enough for the general principle to hold.

In addition to the advantages just described, hypertrophy also entails significant disadvantages Of these, the most important is that the greater thickness impedes the metabolic exchanges between the muscle fibers and the capillaries, which run longitudinally between them, and thereby predisposes to inadequate nutrition and consequent failure (page 335). Further, in the experiments of Hasenfeld and Romberg[29] cited above, the investigators thought they found evidence that hypertrophy interferes with the ability of the heart to increase its diastolic dilatation, which would of itself diminish the reserve force. It might also be thought that the thickening of the walls of the hypertrophied heart would interfere mechanically with diastolic filling. However, the latter conception is hypothetical. The same is true of the possibility, considered by some, that the diastolic tone of the hypertrophied heart is increased and thereby hinders filling; we have seen that the very existence of diastolic tone in the mammalian heart is questionable

The efficiency attained by hypertrophic compensation in some patients is very high. For the compensation to be complete, the reserve force of the heart would have to be as great as it was before the appearance of the circulatory defect for which the hypertrophy compensates In most cases, of course, exercise tolerance tests reveal that so high a degree of compensation is not attained. But there are occasional patients, especially with defects of the aortic valve and hypertension, in whom such ideal compensation is practically attained for a long time, for they can participate in athletics or do hard physical work seemingly as well as ever

So-called Inflammatory and Idiopathic Hypertrophy of the Heart —In the foregoing, hypertrophy has been considered entirely as an adaptation to a disproportion between the functional capacity of the heart and the work thrust upon it There have, however, been a number of attempts to show that the stimulus to growth of the cardiac muscle fibers may also lie in moments not correlated with functional inadequacy of the heart While none of these carry conviction, they continue to be cited in the literature, and therefore may be mentioned briefly here

In an extensive investigation, Albrecht[1] supported the thesis that cardiac hypertrophy is a manifestation of parenchymatous inflammation, the enlargement of the muscle fibers being a reaction to "nutritive stimulation " The evidence adduced by Albrecht in favor of the inflammatory nature of cardiac hypertrophy consists largely in changes in the heart muscle cells and the interstitium which he interpreted as inflammatory. He also believed that the enlargement of the muscle fibers in cardiac hypertrophy results from an increase in the sarcoplasm and not in the actual contractile substance of the fibrillæ, which would indicate that the contractile strength of the fiber is not heightened by its enlargement. However, it has been found that the histological changes which Albrecht interpreted as inflammatory are secondary and inconstant, developing with further dilatation and failure, and it has also been shown that the contractile substance (fibrillæ) is increased in the hypertrophic heart (page 317) The theory of cardiac hypertrophy as a manifestation of parenchymatous inflammation is thus without support

"Idiopathic" Hypertrophy of the Heart.—Under the name of idiopathic hypertrophy of the heart, Bauer and Bollinger[7] described the great frequency of marked cardiac hypertrophy among Bavarians who drink enormous quantities of beer, 10 or more liters daily, over a period of years. The condition is also known as the Munich beer heart or the Tuebingen wine heart. The conception was that the consumption of such great quantities of the highly nutritious Munich beer, or of wine, in addition to ample other food taken with it, led to plethora and to increase in the mass of the heart through the excessive quantity of foodstuffs brought to the organ. However, subsequent investigations of these cases by Moenckeberg,[51] Romberg[57] and others have shown that in most instances there is arterial hypertension, which would seem to be primarily responsible for the hypertrophy. It would seem probable that various pathogenetic factors are concerned in the production of these cases of "idiopathic" cardiac hypertrophy or beer heart. The primary moment in most instances is doubtless the arterial hypertension just mentioned. If, as has been assumed, such immoderate beer drinking increases the circulating blood volume over a large portion of the day, this factor may also be concerned in the production of cardiac hypertrophy and ultimate failure. Most often, the individuals in question are obese and they frequently have arduous occupations, which may also predispose to hypertrophy and failure. From the descriptions of the anginal attacks in such cases, it seems likely that many of them also have coronary arteriosclerosis. That alcohol specifically damages the heart has not been demonstrated. In the only case that I have seen that might have been classified as a "beer heart," which concerned a stoker in a brewery who drank almost unbelievable amounts of beer while in the hot stokeroom, there was both hypertension and coronary arteriosclerosis.

Another variety of case that has been included in the rubric of idopathic cardiac hypertrophy is the so-called *congenital idiopathic hypertrophy* of the heart, in which very large hearts are encountered in infants. Fifty-two such cases are collected in Kugel and Stoloff's[45] papers to which the reader is referred for a detailed discussion (see also Crawford and Weiss[17]). It appears that in the large majority of cases there are either inflammatory or degenerative changes in the myocardium, or there is a renal or other extracardiac cause for the hypertrophy.

To be differentiated from cardiac hypertrophy is the enlargement of the heart that occurs in von Gierke's disease, an obscure metabolic disorder of infancy and childhood in which enormous deposits of glycogen occur in various organs. The deposition of glycogen in the heart may lead to massive cardiac enlargement and heart failure; some of the cases have doubtless been included in the rubric of congenital cardiac hypertrophy in the past (Antopol, Heilbrunn and Tuchman[3]).

Pathological Anatomy of Cardiac Hypertrophy.—Cardiac hypertrophy consists in an increase in the mass of the muscle of one or more chambers. In fact, it is even more selective in its localization than is implied by the involvement of individual chambers, for Kirch[42] has found that, like dilatation, hypertrophy of the left ventricle due to hypertension or aortic defects always starts in the outflow tract of the left ventricle and only subsequently involves the inflow tract.

As a rule, cardiac hypertrophy is evidenced by thickening of the wall of the involved chamber, although it must be remembered

that postmortem contraction can simulate thickening of the myocardium. But if the concomitant dilatation is marked, the hypertrophied wall may be thinned to even less than the normal thickness. In such cases, weighing the heart generally demonstrates the hypertrophy. Relatively slight degrees of hypertrophy of one chamber can be demonstrated only by dissecting the individual parts of the heart and weighing them separately according to the method of Mueller[64] or by careful linear measurements with the technic of Kirch. The reader is referred to the original publications for details of these methods, which have contributed much to our knowledge of the pathological anatomy of heart disease but are too laborious for ordinary necropsy work.

Not only is the wall of the chamber increased in mass when it is hypertrophic, but the papillary muscles, columnæ carnæ, and musculæ pectinatæ are likewise enlarged. In fact, one can often detect the presence of hypertrophy, when it is doubtful from the thickness of the wall, by the massivenss of the papillary muscles and the unusual projection of the thick, rounded trabeculæ with deep recesses between them. But when the hypertrophy is accompanied by marked dilatation, the papillary muscles may become attenuated and the trabeculæ flattened

The size of the cavity of a hypertrophic chamber is determined by the amount of concomitant dilatation. In most instances, the enlargement of the cavity is immediately obvious. However, there are also instances of hypertrophy in which the increased capacity of the chamber is not evident, although we have seen that it seems highly probable that hypertrophy always develops on the basis of some dilatation That hypertrophy of the wall ever notably diminishes the size of the cavity (concentric hypertrophy) by centripetal thickening is very improbable, although sometimes at necropsy, as a result of postmortem contraction, the cavity of a ventricle is almost obliterated However, marked thickening and bulging of the septum in left ventricular hypertrophy may impinge notably on the lumen of the right ventricle (page 447).

Hypertrophy may result in enormously massive hearts. The wall of the left ventricle may be thickened to over 30 mm. and that of the right ventricle to over 12 mm. The auricles, especially the left in mitral stenosis, may be three or four times the normal thickness. Heart weights of 600 grams are not uncommon and even over 1000 grams is not excessively rare as a result of universal hypertrophy. Stokes[65] observed a heart which attained the prodigious weight of 1980 grams. In general, a heart weighing 400 grams in the male or 350 grams in the female is hypertrophied. Since Laennec, the size of the normal heart has been considered as approximately that of the right fist of the cadaver. However, the heart weight and size must be interpreted in the light of the

general habitus and muscular development of the individual; in persons of asthenic constitution, much lighter hearts may be definitely hypertrophied, especially if the hypertrophy is confined to one chamber. In general, hypertrophy evolves more rapidly and attains a greater mass in the young, but enormous hearts are also observed to develop after middle life. In most instances in which massive cardiac hypertrophy is present, more or less cardiac insufficiency has existed for years, the patient being generally on the verge of complete incapacity, punctuated by repeated and protracted periods in which the heart failure is severe enough to keep the sufferer in bed The statistics of Cabot[12] show that very massive hearts, approaching 1000 grams, are most common in adhesive mediastino-pericarditis. Diseases of the aortic valve and less often—perhaps because of the more advanced age incidence—arterial hypertension are also potent causes of the *cor bovinum.* The proportion of cases of mitral disease, and especially of cardiac insufficiency secondary to thyrotoxicosis or pulmonary lesions, in which such massive hypertrophy develops is much smaller For detailed statistics, the reader is referred to the above-mentioned book of Cabot.

With the onset of general cachexia, cardiac hypertrophy may regress to some extent. I have seen at least two examples of such atrophy of a previously hypertrophied heart in patients with long-standing hypertension who succumbed to cancer; in both instances, the shrinkage was evidenced by tortuosity of the coronary arteries. Nevertheless, cachectic individuals sometimes have enormous hearts.

Hypertrophy of the individual chambers causes characteristic changes in the form of the heart, which will be discussed in connection with the roentgen findings (page 362). Here it may be remarked that when the left ventricle is hypertrophied, the apex is generally displaced downward and to the left, the heart as a whole appears more conical, and more of the left ventricle is visible *in situ* following removal of the breast plate. On the other hand, when the right ventricle is hypertrophied, the heart is broadened, the right border is displaced to the right, there is a bulging of the conus arteriosus of the right ventricle to the left, and a considerable portion of the left border is formed by the right ventricle; in extreme instances, the apex is formed by the right ventricle and the left ventricle can hardly be seen in the situs at necropsy. When the right ventricle is hypertrophied, the heart is rotated to the left and backward (page 370), which also helps to displace the left ventricle from the anterior surface.

Hypertrophied heart muscle feels very firm; this is usually most striking in the right ventricle which, if greatly hypertrophied, maintains its form and does not collapse when opened. But post-

mortem changes may soften the hypertrophied myocardium. The muscle substance appears glassy and of a brownish-red color. Both color and appearance are affected by the hemoglobin content of the blood and by such secondary changes as fatty infiltration, pigment deposition, ischemic necrosis, and scarring The hypertrophied papillary muscles often show these degenerative changes most clearly; not uncommonly, fatty change is first perceived in the subendothelial portions of the right ventricle.

Histologically, cardiac hypertrophy is characterized by an increase in the thickness of the individual muscle fibers Formerly, it was thought that the increased mass of the hypertrophic heart results from hyperplasia of the muscle cells. However, the investigations of Letulle,[47] Goldenberg,[28] Tangl,[65] and others long ago showed conclusively that cardiac hypertrophy is almost entirely or perhaps exclusively due to increase in the average size of the muscle cells, and not to an increase in their number Nuclear division or other evidences of hyperplasia of the muscle cells are not encountered in the hypertrophied heart. Letulle found that while normally the average diameter of the muscle fibers is between 15 and 20 microns, in hypertrophied hearts it is most often above 25 or 28 microns The quantitative studies of Karsner, Saphir and Todd[38] indicate that in cardiac hypertrophy the muscle fibers tend to increase in thickness to a uniform limit. What conditions this maximum thickness is not entirely clear; possibly, it is related to the nutrition of the cell, which is derived from capillaries running between the fibers. There is hypertrophy of all the elements of the muscle cells, the nuclei being enlarged, the sarcoplasm more abundant, and the fibrillæ more numerous and massive than normally (Aschoff and Tawara[4]) In the cardiac hypertrophy of aortic regurgitation, Stadler[62] also found evidence of increase in the length of the fibers, for the central nuclei were further apart than in the non-hypertrophic parts of the heart. It may be that this lengthening is an *evidence of dilatation; in experimental hypertrophy without significant* dilatation, Rytand and Dock found indirect evidence that hypertrophic fibers may be decreased in length (page 311). Aschoff and Tawara, Keith and Flack[40] and Moenckeberg[52] have found that the fibers of the conduction system do not participate in cardiac hypertrophy.

The behavior of the connective tissue in the hypertrophied heart has been extensively investigated, particularly as regards its relation to heart failure From the anatomical point of view, Letulle long ago divided cardiac hypertrophy into two stages, in the first of which there is only enlargement of the muscle fibers, while in the second there appears in addition regressive changes in the fibers and connective-tissue hyperplasia Similar observations were made by Dehio.[21] He found that as long as the hypertrophy

is not accompanied by noteworthy dilatation, connective-tissue proliferation is absent, but with dilatation interfascicular and intercellular hyperplasia of connective tissue appears Subsequent studies by Jacobi[37] have shown that this hyperplasia involves not only the collagenous tissue but also the reticulum fibers, although the elastic tissue is not notably increased. Dehio found that while this *myofibrosis cordis* is diffusely distributed, it varies in degree in the different parts of the heart, the auricles are more severely affected than the ventricles The observations of Moenckeberg on hypertrophic human hearts and of Stadler and Jacobi on hypertrophy in experimental aortic and tricuspid lesions also revealed a parallelism between dilatation and the extent of connective-tissue hyperplasia

From these observations it seems clear that cardiac hypertrophy is not necessarily accompanied by any considerable hyperplasia of the interstitial connective tissue, but that the latter process is rather correlated with dilatation The nature of this correlation has proved a knotty problem, and will be considered in conjunction with the anatomical findings in heart failure (page 328).

UTILITY AND CORRELATION OF THE CARDIAC COMPENSATORY MECHANISMS

The three mechanisms which tend to increase the accomplishment of the strained heart have been described in the preceding sections It may be well, at this point, to summarize the advantages and disadvantages of each of these mechanisms and their correlation with one another.

Tachycardia.—When a ventricle fails, the engorgement upstream to the failing chamber ensures rapid diastolic filling and consequently provides the condition most favorable to augmentation of output by acceleration in rate up to certain limits (page 294). When tachycardia in heart failure is not excessive, it thus tends to eliminate the engorgement upstream to the failing chamber which probably elicits the acceleration in rate through reflex mechanisms—an example of the reflex autoregulation of the circulation under pathological circumstances Tachycardia has the further advantage that it can be called into play immediately. On the other hand, tachycardia has serious disadvantages. It entails the shortening of diastole, the rest period of the heart, and thereby predisposes to fatigue and failure. This is especially important when the heart is dilated or hypertrophied. For when the heart is dilated, its oxygen requirements are correspondingly higher And hypertrophied heart muscle not only requires a more abundant blood supply, but the greater thickness of the muscle fibers necessitates a longer rest period for adequate metabolic exchange with

the blood (page 336). It is therefore not surprising that protracted tachycardia generally results in intensification of heart failure.

Dilatation.—Dilatation increases the systolic accomplishment of the ventricle. This and the rapidity with which it is called into action are its advantages But dilatation has the great disadvantage that it entails elevation of pressure in the dilated ventricle during diastole. A necessary consequence is engorgement and rise in pressure in the segment of the vascular bed upstream to the dilated ventricle. When the left ventricle is dilated, there is engorgement and hypertension in the pulmonary circuit, which is the prime cause of cardiac dyspnea. When the right ventricle is dilated, there are engorgement and rise in tension in the systemic veins, which lead to edema and swelling of the liver While dilatation serves to increase the cardiac output, it thus leads to the accumulation of blood and rise in pressure upstream to the dilated chamber which are the immediate causes of most of the cardinal symptoms of heart failure.

Hypertrophy.—This represents the most advantageous of the compensatory mechanisms for two reasons. (1) Hypertrophy does not involve the shortening of the rest period of the heart and consequent predisposition to fatigue that does tachycardia, and (2) hypertrophy increases the energy and accomplishment of systole without requiring, as does dilatation, the increase in the diastolic pressure within the ventricle that leads to engorgement upstream to the failing chamber When hypertrophy is adequate, the circulation returns to normal except that the pressure within the hypertrophied ventricle is increased during *systole* While hypertrophy is thus the ideal *compensatory mechanism,* it takes time to evolve and therefore comes into action only after a considerable lapse of time Furthermore, because of the greater requirement of blood supply and the disadvantageous conditions for metabolic exchange, hypertrophy carries within it the germs of ultimate failure

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CHAPTER XIX

THE MECHANISMS OF HEART FAILURE

FUNDAMENTAL among the problems of cardiovascular pathology are those of the immediate causes of heart failure. Why, for example, does an individual who has had aortic regurgitation for many years without being short of breath, suddenly or gradually develop the symptoms of an insufficient heart and succumb, although the necropsy shows that the valvular defect has undergone no essential change for a long period before death? The problem has been investigated from a number of points of view, and considerable information obtained. Nevertheless, as yet the question of why the heart fails cannot be answered in a high proportion of cases. In the following, only a general discussion of the problem will be attempted, postponing more detailed consideration for the sections on the individual diseases.

RELATION OF MORPHOLOGICAL CHANGES IN THE MYOCARDIUM TO HEART FAILURE

In certain instances of heart failure, the anatomical findings seem adequate to explain the cardiac insufficiency. Such, for example, is true in some cases of coronary thrombosis with massive necrosis of large portions of the myocardium. Likewise, when the heart is involved in diphtheria, the damage to the myocardium may be so intense and universal that the cause of the cardiac weakness appears obvious.

However, these cases in which the anatomical basis of heart failure seems adequate are decidedly the exception and not the rule. It is much more common that the damage to the myocardium unveiled at the postmortem table appears insufficient to account for the severe cardiac weakness. In fact, there are many cases of valvular, coronary or hypertensive disease in which the pathologist is unable to determine from the inspection of the heart whether or not the patient suffered from cardiac insufficiency during life; he is forced to inspect the other organs for evidences of chronic passive congestion to recognize that the heart had failed. Even moderate dilatation of one or more chambers of the heart does not prove that it was insufficient, for equal dilatation may be found where the subject had never been short of breath, or may have developed *sub finem vitæ*. The severity of a valvular defect in itself affords no information whether or not heart failure had been present. It is by no means uncommon for very tight mitral stenosis to be

found "accidentally" at the necropsy of individuals succumbing to cancer or other disease without having manifested evidences of an inadequate heart during life. The same is true in coronary artery disease, which may be very severe, cause widespread myomalacia, and myocardial fibrosis without the patient ever having had shortness of breath or other symptoms of cardiac failure On the other hand, there are many individuals with valvular defects, coronary sclerosis or arterial hypertension who suffer from severe heart failure for years and finally are overcome by it, despite the fact that the myocardium reveals little damage on the postmortem table.

It thus seems evident that gross lesions of the myocardium are not responsible for the vast majority of instances of heart failure.

Attempts have also been made to incriminate as the cause of heart failure various lesions of the myocardium revealed by the microscope. An extensive investigation of this type was carried out by Krehl,[48] Romberg,[71] and their associates, who studied histologically a large number of instances of heart failure in valvular defects, renal disease, "idiopathic" cardiac hypertrophy (*i e.*, hypertension), and rheumatic, typhoid, scarlet, and other infectious fevers. In almost all their cases, they found histological evidence of acute or chronic "myocarditis." These consisted in vacuolar, granular, fatty, and other regressive alterations in the muscle fibers with changes in the nuclei which they interpreted as pathological, often culminating in destruction of the muscle substance The parenchymatous alterations were accompanied by interstitial cellular infiltrates and fibrosis as well as lesions of the vessels They believed these changes in the myocardium—which they interpreted as inflammatory—were extensive enough to account for the heart failure. The findings of Krehl and Romberg were confirmed by Albrecht,[1] who believed that the localization of the inflammatory lesions in special parts of the myocardium produces the heart failure.

However, when the question was reinvestigated in great detail by Aschoff and Tawara,[8] they showed very convincingly that, apart from the heart failure of diphtheria, Krehl and Romberg had grossly overestimated the significance of demonstrable histological changes in the genesis of cardiac insufficiency They found that in the vast majority of cases, including rheumatic heart disease in which myocardial changes are practically constant, *histologically demonstrable lesions of the myocardium are entirely inadequate to account for the heart failure* Much more extensive damage of the myocardium is often found in other hearts which were entirely competent during life. Similar observations were made by Clawson[13] in an anatomical study of heart failure in essential hypertension, chronic glomerulonephritis, right ventricular hypertrophy, defective valves, luetic aortitis, and adherent pericardium. He also arrived

at the conclusion that "myocardial failure is rarely due to anatomical changes in the myocardium."

In the following sections, we will consider the relation of certain of the individual anatomical findings to cardiac failure.

Fatty Change.—"Fatty degeneration" of the heart muscle was formerly highly esteemed as a cause of heart failure; in Stokes[31] and other older classics on heart disease, special chapters are devoted to the clinical picture of the fatty heart. The Stokes-Adams syndrome was erroneously considered a manifestation of fatty heart. However, recent investigators regard increase in the amount of lipids demonstrable microscopically as of relatively little significance for the function of the heart muscle. In the past the diagnosis of pathological fatty change was probably made too often, for Master[39] and others have shown that even in health appropriate stains reveal the presence of finely divided fat in the heart muscle

In most instances of heart failure in valvular disease, hypertension, etc., the amount of lipid that can be demonstrated histologically is not strikingly increased. And even when there is extensive accumulation of fatty droplets, it seems improbable that the process is in itself highly deleterious to the heart, although it bespeaks an abnormality in the metabolism of the myocardium. The droplets are located in the sarcoplasm between the fibrillæ in which the contractile function is vested. And when the lipid is removed by passing the section through xylol or other lipid solvents, the nuclei and fibrillæ are generally seen to be little altered The slight significance of even higher degrees of accumulation of lipids in the heart muscle for cardiac function is shown by the numerous infections, intoxications, metabolic disturbances (notably diabetes) and anemias in which the Sudan stain reveals the heart muscle fibers crowded with fatty droplets, although the heart was functionally adequate

It would therefore seem that steatosis of the myocardium is rarely, if ever, primarily responsible for heart failure. On the contrary, when fatty change is present in chronic heart failure, it is probably a consequence of the latter, just as occurs in passive congestion of the kidneys and other organs. The uneven distribution of the steatosis, often manifested microscopically by alternation of fatty and non-fatty areas producing the appearance of tigering, speaks in favor of the view that the fatty change is a consequence of the circulatory disturbance. For Ribbert[43] and Nussbaum[44] long ago showed by injection of the vessels that tigering is produced by predominance of the steatosis in the areas of poor blood supply around the small veins, while the heart muscle near the small arteries is less affected.

Of course, the fatty change that accompanies severe necrobiotic lesions of the heart muscle, notably in diphtheria, must be differ-

entiated from the type just described. In such instances, the appearance of fat in the muscle fibers is merely one of the phenomena occurring in the course of the process that terminates in cell death; it is the necrosis of the muscle that produces the heart failure.

Another form of fatty change of the heart is that in which the epicardial fat is so increased in amount that it infiltrates extensively between the muscle fibers, in the right ventricle often to the endocardium. The significance of this so-called *adipositas cordis* has been debated; probably, it is only rarely consequential in producing heart failure and is not uncommonly found in high degree in obese individuals who had no symptoms of cardiac insufficiency

Cloudy Swelling.—Separation of albuminous granules in the sarcoplasm producing cloudy swelling is often to be seen when bronchopneumonia or other infections or intoxications accompany the last stages of heart failure. However, cloudy swelling is frequently also found in the absence of heart failure. It would, therefore, appear that cloudy swelling does not necessarily, if ever in itself, indicate severe damage to myocardial function According to Kutschera-Aichbergen,[49] cloudy swelling often develops postmortem; in most instances, he failed to observe it in fresh and well-fixed preparations. The gross appearance of the heart which has undergone considerable postmortem autolysis often closely simulates cloudy swelling

Vacuolar Degeneration.—When chronic heart failure was present it is not rare to find vacuoles filled with fluid in the sarcoplasm Usually, they are not very abundant Aschoff and Tawara regard them as consequences of the venous stasis rather than as causes of the heart failure In favor of this view is their observation that the vacuoles are almost always accompanied by interstitial edema, which they also interpret as a result of the passive congestion of the heart According to Moenckeberg[50] vacuolar degeneration may also accompany inflammatory edema of the heart

Necrobiotic Changes.—On rare occasions, widespread necrosis of the heart muscle is produced by various infections, above all diphtheria, and intoxications, as carbon monoxide poisoning. The necrosis is characterized histologically by various forms of nuclear destruction and by disintegration of the muscle fibers with loss of transverse striation and breaking up of the fibrillæ Sometimes, large areas of the muscle fibers become coagulated into homogenous hyaline masses, which may resemble Zenker's degeneration of the voluntary muscles In other places or in other instances, the products of the disintegration of the nuclei and fibers become aggregated in granular masses. The Sudan stain generally reveals large amounts of stainable lipid, irregularly distributed To these different histological pictures of necrobiosis such terms as hyaline

and waxy degeneration, toxic myolysis, and granular-clumped disintegration have been applied. They are discussed further in connection with the diphtheria heart.

When such necrosis is sufficiently diffuse, which is very rare apart from diphtheria, it furnishes the classical instance of heart failure explained by the anatomical findings in the myocardium But it is worthy of reiteration that these cases are *very* rare in comparison to the totality of instances of heart failure.

Isolated massive infarction of the myocardium due to coronary thrombosis often, though not always, causes heart failure. As a result of repeated coronary occlusions so considerable a proportion of the myocardium may be destroyed and replaced by scar tissue that myocardial insufficiency occurs, another example of heart failure which is adequately explained by the anatomical findings But the cases in which the scarring of the heart muscle is sufficiently widespread to explain cardiac failure are very rare.

Focal necroses of the heart muscle are common as a result of minute thromboses in rheumatic fever and other infections, as well as in uremia Especially in uremia, they may terminate in tiny areas of calcification These focal necroses seem to be of little significance for the genesis of heart failure; they may be numerous in the absence of the latter

Brown Atrophy.—In old age the heart becomes atrophied and dark brown—brown atrophy Similar atrophy occurs in cachexia due to starvation or disease, the diminution in the weight of the heart apparently paralleling that of the skeletal musculature. Diminution in the work of a chamber of the heart leads to selective atrophy of that chamber. The classical example is the left ventricle in "pure" mitral stenosis, but atrophy of the left heart is also observed in unusual instances of kyphoscoliosis and other forms of interference with the pulmonary circulation, as a result of which the left side of the heart receives less blood The atrophy of the heart is due to diminution in the size of the individual muscle fibers. According to the studies of Karsner, Saphir and Todd,[43] the fibers tend to diminish to a uniform thickness Stadler[80] found that the muscle nuclei are closer to one another in the atrophic heart, evidence that the fibers also decrease in length. The fibers of the conduction system do not participate in the atrophy (Moenckeberg[60] and others) The pigmentation of the myocardium, which is most often present in all forms of atrophy, including that due to starvation, is due to the deposition of pigment granules at the poles of the nuclei and, when marked, between the fibrillæ. The pigmentation is merely an accentuation of the physiological occurrence of pigment granules, which begins in the first decade. The pigment gives lipoidal staining reactions but does not react to tests for iron. While its exact nature is in question, it is generally classed with the

"wear and tear" pigments, which bespeak retardation in the removal of katabolic products from the cell

Atrophy of the heart is doubtless accompanied by diminution in its functional capacity, for a fundamental determinant of the contractile strength of a muscle is its cross-section. However, the circumstances in which atrophy occurs, enumerated in the preceding paragraph, are such that the demands on the heart are proportionately diminished. The result is that one often sees at the necropsy of aged individuals very marked brown atrophy although there are no evidences of heart failure. However, it seems very probable that when the demands on an atrophic heart are increased, as in the presence of bronchopneumonia or another infection, cardiac insufficiency may develop more readily than if the heart were more massive. Atrophy of the heart is presumably of significance in the genesis of the cardiac insufficiency that sometimes terminates protracted cachexias. In instances of sudden death in old persons, brown atrophy of the heart is sometimes considered by the medicolegal examiner as an adequate explanation for heart failure, but whether this is justified is questionable

Interstitial Cellular Infiltration.—Much the most important and common form of myocarditis is that occurring in rheumatic fever and characterized histologically by the Aschoff body (page 340). However as Aschoff and Tawara[3] pointed out, rheumatic myocarditis is primarily interstitial, predominantly perivascular, and very rarely so extensive as to compromise enough of the myocardium to come into consideration as the essential cause of heart failure. Moreover, in most instances of rheumatic heart disease there is little, if any, diffuse degenerative change in the muscle fibers. Aschoff and Tawara also showed that while the healing of rheumatic myocarditis results in numerous perivascular scars, the surrounding muscle is unaffected by the process The same is true of the minute necroses following occlusion of small vessels which they found very frequently in rheumatic hearts The result is that while repeated attacks of rheumatic fever may leave a large number of scars in the heart, the proportion of the heart muscle that suffers is generally very small. All in all, the conclusion reached by Aschoff and Tawara thirty-five years ago, that *cardiac failure in rheumatic heart disease is rarely explained by the anatomical findings in the myocardium*, seem well substantiated. The very rare exceptions are fulminating cases of rheumatic fever which run very high fever and rapidly succumb to heart failure In such cases, mostly in children, the myocarditis may be sufficiently diffuse to account for the cardiac insufficiency. Of course, appropriately localized lesions may cause change in the rhythm of the heart, which may impair its functional capacity

In other infections, apart from diphtheria (page 588), it is ex-

tremely rare for myocarditis to be severe and diffuse enough to afford an adequate *anatomical* basis for heart failure. In Chapter XXXII it will be seen that the common infections other than rheumatic fever and diphtheria rarely lead to the failure of a previously healthy heart—most of the clinical pictures formerly attributed to infectious "myocarditis" are really examples of peripheral circulatory failure—and that even when this occurs an adequate anatomical basis in the form of inflammatory changes more severe than those found in the same disease without heart failure is generally absent. The few cases of myocarditis of unknown etiology leading to heart failure are discussed on pages 313 and 587, and the much-debated syphilitic myocarditis on page 466.

In rare instances, malignant growths or leukemic proliferations infiltrate the myocardium diffusely. But it is extremely rare for heart failure to result, although they may lead to disturbances in rhythm.[23]

Interstitial Fibrosis.—The healing of rheumatic myocarditis leads to interstitial fibrosis. But this fibrosis is focal in distribution and, according to the studies of Clawson,[13] rarely more than slight in extent. It appears from the literature (Moenckeberg[62]) that diphtheritic myocarditis is followed in rare instances by widespread fibrosis of the heart, the same is true to a much less extent of the myocarditis due to scarlet fever and other infections. However, even when such post-inflammatory fibrosis is extensive, it is not to be regarded as the cause of arrhythmias or heart failure that may be present, the latter are the result of the destruction of muscle fibers for which the connective tissue substitutes spatially, or due to renewed damage to the surviving heart muscle.

A problem that has long excited controversy is that of the significance of the interstitial fibrosis that is so common in cardiac hypertrophy resulting from essential hypertension or, much less often, from emphysema or other forms of increased resistance in the pulmonary circuit. The fibrosis has been considered a replacement fibrosis for degenerated muscle and also a consequence of stretching of the muscle fibers. It has also been thought that the interstitial fibrosis is a consequence of chronic passive congestion of the heart, just as fibrosis develops in other passively congested organs. But the latter cannot be the whole explanation, for the fibrosis is more marked in the dilated chamber than in the others. Clawson[13] believes the fibrosis to be the result of coronary artery disease, having found no evidence that myocardial strain in itself causes fibrosis. He observed that when cardiac failure results from glomerulonephritis, and there is no coronary arteriosclerosis, myocardial fibrosis is also absent. There is, of course, no doubt of the causative rôle of coronary artery disease in the production of discrete foci of fibrosis following focal myomalacia, which may be very numerous

And in all probability coronary narrowing is an important factor in the production of many instances of the diffuse myocardial fibrosis now under discussion. But diffuse fibrosis may also be present in dilated hypertensive hearts in which coronary sclerosis is not sufficient to narrow significantly the lumens of the vessels Jacobi[41] observed the development of extensive diffuse fibrosis within a few weeks of the production of the experimental aortic regurgitation, in which there was no lesion of the coronary arteries To the writer, it would appear probable that the diffuse fibrosis in question is a consequence of relative ischemia of the hypertrophied heart muscle due to the coronary flow not being augmented sufficiently to keep pace with the increase in the mass of the myocardium and the greater amount of work it performs. To a certain extent, the fibrosis may fulfill a compensatory function in preventing rapid and excessive dilatation of the overburdened chamber But that the fibrosis as such plays any part in the production of heart failure is not evident

Fragmentation and Segmentation.—These terms are applied to a transverse splitting of the heart muscle fibers Fragmentation designates splitting in the general course of the fiber, while segmentation means that the splitting is along the transverse lines (intercalated disks). Segmentation appears to be rare, in fact, Aschoff and Tawara[3] doubt that the splitting ever actually passes through the transverse lines. The phenomenon is rare in the young but becomes increasingly frequent with advancing years, Aschoff and Tawara found it in two-thirds of adults Fragmentation involves only the ventricular myocardium, the papillary muscles of the left ventricle constitute the site of predilection (Moenckeberg[61]) Lissauer[55] states that the specific muscle of the conduction system is not affected. The course of the fractures is generally somewhat oblique and may be step-like. They do not always cross the entire width of the fiber. The nuclei are not involved.

The cause of fragmentation has evoked much discussion The fractures are not postmortem artefacts, they have been observed in hearts fixed very soon after death, and it has not been possible to produce them by postmortem manipulation of the heart. On the other hand, the total absence of reaction around the splits indicates that they did not exist long during life In fact, widespread fragmentation would scarcely seem compatible with prolonged function of the myocardium It is therefore now generally agreed that fragmentation is an agonal phenomenon. Fragmentation does not seem to be related to any specific lesion of the myocardium, being found in individuals succumbing under various conditions and without any definite heart disease. Fragmentation was formerly considered to be especially common and well marked in instances of sudden death, but this has not been established However, the fact that fragmentation is rare in the young and becomes common

with advancing years may indicate that regressive changes in the myocardium predispose to it, although Aschoff and Tawara found no evidence that the lesion is more common in the presence of fatty change or edema Most recent investigators (Moenckeberg[21]) believe that perverse contractions of the heart muscle at the end of life produce the lesion. It is possible that fibers which are devitalized first are torn by contractions of the neighboring fibers. Moenckeberg's suggestion that fragmentation may be the anatomical expression of terminal ventricular fibrillation is very interesting and worthy of further investigation.

THE RÔLE OF MYOCARDIAL FATIGUE IN HEART FAILURE

From the foregoing, it seems clear that *the known morphologic changes in the myocardium do not suffice to explain the large majority of instances of heart failure* For this reason, recent investigators have endeavored to elucidate the pathogenesis of heart failure along primarily *functional* lines The conception which seems most probable in the light of available evidence is that *heart failure is most often the result of a change in the metabolic state of the heart muscle analogous to what is known as fatigue in skeletal muscle, and that this altered metabolic state is characterized by decreased efficiency, i. e., by diminution in the proportion of liberated energy which is converted into mechanical work.* In the following, we will first discuss the evidence in favor of this conception, and then describe the processes which may favor fatigue of the heart muscle.

Most often, heart failure succeeds a more or less protracted period of cardiac strain Before the heart gives way, it has generally performed increased work for a considerable time and thereby mastered the greater load due to high blood pressure, valvular defects, emphysema, etc Very often it appears clear that neither the load of the heart nor the morphology of the myocardium has changed for a considerable time before or during the transition from excellent compensation to severe heart failure Consideration of these facts naturally leads to the conception that the failure of the heart may be due to fatigue of the overworked myocardium, just as skeletal muscle tires if it works too long or too hard. The researches of recent years on muscle physiology have shown that there is a fundamental and far-reaching similarity in the nature of the contraction process in skeletal and cardiac muscle—as would be anticipated from their close morphological resemblance—and it would therefore seem probable *a priori* that the manifestations of exhaustion in both varieties of muscle should be much akin. That such is actually the case is indicated by a variety of evidence, some of which will be found summarized in the brilliant monograph of Harrison[23] and the article by Kutschera-Aichbergen.[44]

In favor of the view that clinical cardiac failure is at least often a process analogous to what is called fatigue in skeletal muscle, the following arguments may be advanced.

1. Rest is the sovereign therapeutic agent in heart failure. Conversely, increase in the work of the heart intensifies and protracts cardiac failure. This behavior is analogous to that of skeletal muscle, which recovers from fatigue with a rapidity proportional to the completeness of the rest allowed it

2. Digitalis is the supreme pharmacological remedy for combating heart failure This action is so specific that it would seem that when we know how digitalis acts, light will be shed on the intimate nature of heart failure. The action of digitalis, unfortunately, is by no means completely comprehended, but it will be seen in Chapter XXXIV that a fundamental element in the salutary effect of the drug is slowing of the heart with resultant increase in the rest period of the heart. This would accord well with the conception of heart failure as a variety of fatigue. Moreover, there is some evidence that digitalis bodies hinder fatigue in skeletal muscle (Neuscloss[63]).

3 In experiments on the heart-lung preparation as carried out by Starling and others (page 300), after the heart has been working efficiently for some time it begins to weaken and this weakening becomes more pronounced until the heart fails completely. Under the conditions of the experiment, the weakening is to be attributed to fatigue of the myocardium. The fatigue is manifested first by dilatation of the heart, which increases gradually and is accompanied by higher venous pressure although the output of the heart is for some time maintained at the previous level. Gradually the dilatation becomes more and more marked until a stage is reached in which the output of the heart progressively diminishes, ultimately reaching complete failure. These successive manifestations of fatigue in the isolated heart closely resemble the course of events in clinical heart failure, and it therefore seems highly probable that the latter is also to be viewed as a form of myocardial fatigue.

From a number of points of view, then, there are strong indications that heart failure is due to a change in the functional state of the myocardium akin to what is termed fatigue in skeletal muscle. Nevertheless, while the conception of heart failure as a variety of *myocardial fatigue is important from therapeutic and other points of* view, the actual nature of the process still remains to be elucidated. As Harrison, who has done much to further the conception of heart failure as *myocardial fatigue*, says in this connection, "A name is not an explanation." For despite the great recent advances in comprehension of the chemical changes occurring in muscular contraction, the causation of fatigue in even skeletal muscle is not understood. Among the factors that may be concerned are

the accumulation of katabolic products, the exhaustion of the substances from chemical transformation of which the energy for muscular contraction is derived, and the production of specific "fatigue substances" It has been thought that the development of tissue acidosis is of especial significance in the production of fatigue But these are all hypotheses, and even less is known about the nature of fatigue in heart muscle In experiments with excised hearts, it has been found that fatigue can be accelerated by deficiency of blood supply, oxygen, or various lipids, as well as by changes in reaction and in the concentration of the individual ions (see the reviews of Wiggers,[91] Tigerstedt[89] and Kutschera-Aichbergen[49]), but the relation of these experimental findings to human heart failure remains to be elucidated

The Decreased Mechanical Efficiency of the Failing Heart.—Perhaps the best available lead in the search for the nature of the alteration in the functional state of the heart muscle which leads to fatigue and failure is the finding that the mechanical efficiency of the failing myocardium is decreased Investigations on the surviving mammalian heart (Rohde[79]) and the mammalian heart-lung preparation (Evans and Matsuoka[21] and Gremels[26]) have shown that as the heart fails, it consumes more oxygen for the performance of the same amount of work, *i. e.*, the mechanical efficiency is decreased Starling and Visscher[81] found that the increase in oxygen consumption as the heart fails in the heart-lung preparation is proportional to the dilatation. This proportionality of oxygen consumption and diastolic volume of the failing heart has been confirmed by Hemingway and Fee[38] and Peters and Visscher[67] The latter investigators have shown that if the diastolic volume of the heart in the heart-lung preparation be kept constant by changing the venous return, the oxygen consumption remains unchanged as the heart fails but the amount of work decreases, *i e*, there is a decrease in mechanical efficiency, which is the ratio of work performed to energy liberated. Peters and Visscher have also found that digitalis, the outstanding remedy for heart failure, increases the mechanical efficiency of the heart.

It would thus appear well established that in at least some forms of heart failure, there is a decrease in the efficiency of the heart considered as a machine doing work. But regarding the more intimate nature of the changes in the metabolic state of the heart muscle which decrease its efficiency and lead to fatigue and failure, practically nothing is known

Chemical Studies of the Myocardium in Heart Failure.—It has been thought that chemical studies of the myocardium may throw light on the more intimate nature of heart failure.

Recent investigations have brought forward strong evidence that at least a large portion of the energy for the contraction of the

skeletal muscle is derived from the decomposition of phosphocreatin. It has also been found that there is some parallelism between the functional state of skeletal muscle and its creatin content, in various conditions of muscular asthenia the creatin content of the muscles is low, while the increased functional capacity induced by training is accompanied by an augmentation of the creatin content In the light of these facts, it seems very significant for the problem of heart failure that Cowan,[16] Herrmann[39] and his co-workers, and Linegar[54] *et al.*, have found that in human heart failure the creatin content of the ventricular myocardium is less than normal, the observations of Bodansky and Pilcher[7] point in the same direction Herrmann and his associates further showed that (1) There is decrease in the creatin content of the rabbit's heart which has been perfused until it fails and of the heart of the rabbit with experimental myocarditis; and (2) the heart rendered hypertrophic by an experimental aortic valvular defect and the digitalized heart have an increased creatin content Herrmann and his associates believe it probable that the low creatin content of the failing heart is due to suboxidation, possible mechanisms for such suboxidation will be considered in the next sections

The lipid content of the heart muscle has also been investigated Clark[12] showed that the lipid content of the myocardium falls in the course of perfusion of the excised heart, and that the addition of various lipids to the perfusion fluid helps to restore the fatigued heart. Kutschera-Aichbergen found that the phosphatid content of the myocardium is diminished in heart failure, the loss of phosphatid being most marked in the chamber under strain

Detailed studies on the inorganic bases of the myocardium in heart failure have been carried out by Harrison[36] and his associates They find that the potassium content of the heart muscle is diminished in cardiac failure. According to these investigators, the diminution in potassium involves the left ventricle in left ventricular failure and the right ventricle when this chamber has been subject to strain Calhoun, Cullen and Harrison[10] found evidence that the depletion of potassium is an indication of overwork of muscles, for they showed that when skeletal muscle is overworked the potassium content falls. They believe that the loss of potassium results from local acidosis due to oxygen want, and that the consequent deficiency of base predisposes to fatigue Wilkins and Cullen[93] confirmed the depression of the potassium content of the insufficient myocardium and also found a diminution in phosphorus and magnesium, occasional tendency to decrease in calcium and total base, and increase in sodium Kutschera-Aichbergen[49] likewise found diminution in the calcium content of the heart muscle in some, although not all, instances of heart failure In experiments with excised hearts, Clark[12] showed that the heart loses calcium as

it becomes fatigued and can be strengthened by the addition of calcium to the perfusion fluid. On the other hand, Scott[76] found no relation between the water, ash, calcium, magnesium, potassium, and sodium content of the myocardium and disease. However, some of his methods have been criticized adversely by Wilkins and Cullen.

These investigations represent the pioneer attempts to learn the chemical and physico-chemical changes in the myocardium in heart failure, a line of investigation from which much is to be anticipated in the future In the light of present conceptions of the physiology of the contraction of skeletal muscle, the observations that the creatin and phosphorus contents of the failing heart are depleted seem especially promising. However, attractive as is the hypothesis, without further evidence it would be premature to assume that depletion of the phosphocreatin content of the myocardium is concerned in the pathogenesis of myocardial fatigue and consequent heart failure The entire subject is as yet in its infancy.

MECHANISMS LEADING TO MYOCARDIAL FATIGUE

Myocardial fatigue and consequent heart failure may be precipitated through either decrease in the functional capacity of the myocardium or increase in the load of the heart. The following sections will consider briefly some of the mechanisms which thus lead to heart failure, as well as some of the circumstances in which it is precipitated. More detailed consideration of the pathogenesis of heart failure will be postponed to the chapters on the individual forms of cardiac insufficiency.

Inadequate Blood Flow.—Ample blood flow is indispensable for muscular activity, and diminution in blood supply quickly leads to fatigue. This is painfully evident if one attempts to exercise the hand with a constricting cuff around the arm. The experiments of Visscher[39a] afford a good illustration of the deleterious effect of diminution in blood supply on the contraction of the heart. Working with the heart-lung preparation, he showed that constriction of the coronary arteries with pitressin or partial obstruction of their lumens with aluminum hydroxide quickly entails weakening of the myocardium, as evidenced by augmentation of the diastolic volume of the heart performing a constant quantity of work. Likewise, in human pathology there is good evidence that inadequacy of the metabolic exchanges between the myocardium and the capillaries due to deficient blood supply is concerned in the pathogenesis of many instances of cardiac failure, especially the decompensation of the hypertrophied heart. This may occur in two varieties of circumstances.

1. Where the blood flow through the entire coronary system or individual coronary arteries is subnormal. Such decrease in blood flow may result from constriction of the coronary lumens due to arteriosclerosis and perhaps thrombosis along the course of the vessels or stricture of their mouths by the scars of syphilitic aortitis In free aortic regurgitation the low diastolic pressure in the aorta may well cause inadequate coronary flow. It is to be presumed that in peripheral circulatory failure with shock the diminished venous return to the heart lessens coronary flow and may thereby lead to cardiac weakness.

2. It seems probable that even though the coronary lumens are not compromised to a high degree or at all, the volume of blood flow required by the hypertrophied heart performing increased work may be greater than that actually delivered. There is then *relative* inadequacy of the blood supply, which favors myocardial fatigue and consequent heart failure. That this mechanism may be concerned in the failure of the hypertrophied heart was long ago suggested by Eppinger and Knaffl[20] and recently supported by the studies of Harrison[14] and his associates.

At least three correlated and overlapping factors tend to increase the volume of blood flow required by the hypertrophic heart:

(*a*) When a hypertrophied chamber performs increased work to overcome, for example, hypertension' or a valvular defect, the oxygen consumption is correspondingly augmented. While this may be partially accomplished by more effective utilization of the coronary blood (greater arteriovenous oxygen difference), heightened metabolism generally necessitates greater blood flow.

(*b*) The nutrition of the larger muscle mass similarly necessitates more blood flow.

(*c*) In hypertrophy, the cross-section of the individual muscle fibers is increased. Harrison, Ashman and Larson[14] point out that since the muscle fibers derive their nutrition from adjacent capillaries, a process in which the physical diffusion of oxygen plays an important part, it seems likely that a longer time is required for completion of the metabolic exchanges with the blood than with fibers of normal thickness. Such retardation of the metabolic exchanges entails a prolongation of the recovery period The latter is especially disadvantageous for the failing heart, whose diastolic rest period is usually abbreviated by tachycardia Harrison and his associates have shown that in various species of animals the cross-section of the myocardial fibers and the length of diastole are adapted to one another; in animals with rapid heart action and consequently short diastole, the heart muscle fibers are thin. In the hypertrophied heart, this adaptation is disturbed by the greater thickness of the muscle fibers without a corresponding augmentation of diastole; on the contrary, the latter is often shortened

Harrison has found that in complete heart block, where diastole is long, cardiac failure is exceptional despite long-standing strain and hypertrophy. His conclusion that disproportion between the cross-section of the myocardial fibers and the length of diastole hampers the nutrition of the heart and is thus an important factor in the pathogenesis of myocardial fatigue and consequently heart failure would seem strongly supported.

The hypertrophied heart thus requires a greater blood flow, probably even proportionately more than the increase in mass. This factor may well set a limit to the extent that hypertrophy is efficacious as a compensatory mechanism; beyond this limit, the heart would "outgrow" its blood supply and therefore be liable to fatigue and failure. That this does not occur earlier is probably due to augmentation in coronary flow that is indicated in many instances by the anatomical findings. Gross[27] has shown by injection of the vessels that the capacity of the arterial tree in the hypertrophied portions of the heart is increased. Russow[44] has found that the total cross-section of the primary coronary branches is augmented in hypertrophic and diminished in atrophic hearts. I have also repeatedly noted in massive hypertrophy of many years' duration that the main coronary trunks are preternaturally capacious. When present, the dilatation of the main coronary trunks doubtless indicates an increase in coronary flow. But it may be doubted that the augmentation of coronary flow keeps pace with the increased demand due to the factors enumerated above, and especially that it is able to atone completely for the retardation of the metabolic exchanges between the thickened muscle fibers and the blood. Further, with the inevitable arteriosclerosis that accompanies middle age, additional increase in coronary flow is prevented even though hypertrophy becomes more massive. This seems a likely explanation of the frequent decompensation of cases of hypertension or valvular disease which have been well compensated by means of hypertrophy for many years, and in which necropsy reveals no severe lesions in the myocardium. Under these circumstances, relatively slight coronary arteriosclerosis with little constriction of the lumen may be much more significant than has generally been realized.

Important evidence indicating that the blood supply *does not* keep pace with hypertrophy of the heart is afforded by the studies of Wearn[63a] and his associates. Comparing 10 normal and 10 hypertrophied human hearts, they found a very evident decrease in the number of capillaries per square millimeter in the hypertrophied hearts. In neither the hypertrophied human heart nor that of the rabbit with experimentally produced cardiac hypertrophy did they find evidence of multiplication of capillaries to compensate for the increase in muscle mass.

When the heart begins to fail and dilates, a relative deficiency in blood supply becomes even more deleterious to the myocardium The experiments of Starling and Visscher[81] on the heart-lung preparation showed that dilatation of the heart is accompanied by a decrease in its mechanical efficiency. They found by studies of the oxygen consumption that as the heart dilates a smaller fraction of the energy liberated is utilized for the performance of work In consequence, the dilated heart requires more oxygen to perform a given amount of work, which presumably entails an increase in blood flow. A vicious circle is thus set up, for the more the heart weakens and dilates, the greater the blood supply it requires.

Another vicious cycle that may develop in the coronary flow of the failing heart is indicated by the investigations of Visscher[82a] Failure of the left side of the heart results in elevation of the diastolic pressure in the left ventricle, failure of the right side of the heart has a similar effect on the pressure in the right ventricle and venæ cavæ. The consequence is tendency to diminution in the pressure gradient along the coronary system, a corollary of which is further impediment to coronary blood flow

An interesting demonstration of the relatively inadequate blood flow to the insufficient heart is afforded by the observations of Kountz and Smith.[47] They perfused human hearts removed soon after death and revived. The coronary flow in healthy hearts was between 0 9 and 1.6 cc. per gram of heart. In individuals succumbing with cardiac failure due to arteriosclerotic, syphilitic or rheumatic heart disease, the flow ranged from 0 15 to 0 60 cc. per gram. This decrease in blood flow per gram of myocardium was due to either narrowing of the coronary arteries or to increase in the muscle mass, in the latter instance, the decrease in flow was sometimes only relative, the total flow being above the usual.

The evidence just summarized renders very plausible the conception that failure of the coronary flow to keep pace with the augmented demands of the hypertrophied heart is often concerned in its eventual failure. But the relative importance of this factor in heart failure other than that due to organic coronary narrowing remains to be determined.

The Rôle of Infection.—The development of an acute infection in a patient with previously compensated heart disease may be quickly followed by cardiac failure This sequence of events is far from invariable; one often sees an individual with hypertension or a high-grade valvular defect pass through lobar pneumonia or gangrenous appendicitis necessitating operation without the least indication of circulatory failure. But in other cases there is no doubt of the causal connection between the infection and the heart failure that follows in its wake. The nature of the connection

between the infection and the heart failure is not always the same and includes the following:

1. The infection may produce severe degeneration and necrosis of so much of the myocardium that the anatomical findings afford an adequate explanation of the heart failure. The outstanding example is the diphtheria heart (page 588).

2. In other cases in which heart failure is undoubtedly precipitated by an infection, the anatomical investigation of the heart muscle does not disclose structural changes in the myocardium sufficiently pronounced to explain the cardiac insufficiency; similar changes are found in individuals succumbing to the same infection without heart failure. This may occur in such infections as pneumonia, influenza and typhoid fever. Most often, those who develop heart failure in this fashion enter their infection with pre-existent hypertension, coronary arteriosclerosis, or valvular defect which had been well compensated, and perhaps unsuspected, until the development of the infection. It seems probable that in these cases heart failure results from a combination of causes: increase in the work of the heart due to fever, functional impairment of the heart muscle emanating from the infection in perhaps the same obscure fashion as does the asthenia of the skeletal muscles, and abbreviation of the rest period of the heart by tachycardia. Because the infections in question produce peripheral circulatory failure far more often that they do heart failure, the latter is discussed in conjunction with shock. (See Chapter XXXII for details.)

3. In individuals with coronary arteriosclerosis, upper respiratory infections or pneumonia may be followed by coronary thrombosis with resultant circulatory failure. Such a sequence of events has been rare in my experience; much more often, pneumonia follows a coronary occlusion.

4. A special and predominant place in the causation of heart failure by infection is occupied by rheumatic fever.

Rheumatic Fever.—The Occurrence of Heart Failure in Rheumatic Infection.—Rheumatic heart disease is the cause of almost all cardiac failure in childhood and adolescence, most of that in young adults, and a small but by no means negligible fraction after the age of forty. This high incidence is not surprising in the light of the great frequency of rheumatic infection and the usual, if not inevitable, implication of the heart. According to Coombs[15] about 75 per cent of individuals with rheumatic infection subsequently exhibit evidences of heart disease. In a large series of cases of rheumatic heart disease studied by De Graff and Lingg,[16] 95.2 per cent developed cardiac insufficiency. In De Graff and Lingg's patients the mean interval between the onset of infection and the first clinical evidences of cardiac insufficiency was eleven years;

22.9 per cent exhibited clinical manifestation of an insufficient heart within a year after infection.

After the symptoms of heart failure have set in, the course is very variable. Some get on well for five or even ten years Others have repeated bouts of heart failure during a period of years, from each of which they recover sufficiently to be up and about, although the tendency is toward a longer duration and less satisfactory improvement with successive attacks Such a protracted course is more common in those who lead a comparatively leisurely life than in the hard-working. Recent studies have shown that, statistically, the prognosis is poor in rheumatic heart disease once the latter has resulted in cardiac failure severe enough to require bed rest Thus, the average duration of life after the onset of heart failure necessitating bed rest was found to be two and a half years by Friedberg and Tartakower[24] and three years by De Graff and Lingg More than 50 per cent of Davis and Weiss'[17] rheumatic patients succumbed within one year after the onset of definite heart failure, 11 of 56 cases with cardiac failure necessitating rest in bed died within one month. These statistics are largely based on hospital material. As intimated above, I do not believe that the prognosis is equally bad in the well-to-do, who can obtain adequate rest and care, although a large series substantiating this opinion is difficult to obtain because of the lesser frequency of rheumatic infection in the financially more fortunate classes. In private practice one not rarely encounters individuals with rheumatic valvular lesions who, notwithstanding shortness of breath and palpitation on mild exertion for over ten years, get along fairly well because they are able to adjust their way of life to the functional capacity of the heart Finally, there are the exceptional cases in which definite rheumatic valvular defects are present for even thirty or more years without heart failure ever developing, the subject finally succumbing to an independent ailment.

Before discussing the mechanism of the failure of the rheumatic heart, it may be well to describe briefly the anatomical picture of rheumatic carditis.

The Rheumatic Lesions of the Heart—Studies by Swift,[85] Talalajew,[87] Klinge,[48] and others have shown that in rheumatic fever there is implication of the connective tissue throughout wide areas of the body, if not universally. The morphological changes seem to be fundamentally similar in all parts, although their form is modified by the terrain in which they develop. It seems probable from the researches of Swift and others that the lesions are the morphological expressions of an alteration in the reactivity of the mesenchymal tissues resulting from the sensitization of the organism to the etiological agent The nature of the latter, whether streptococcal or not, is still *sub judice* and will not be discussed here. Three

stages can be recognized in the natural history of the lesions: an initial stage of degeneration and necrosis of the collagenous connective tissue with fluid and cellular exudation; a secondary stage of proliferation of the fixed connective-tissue cells which in some places agglomerate to form the specific granulomata known as Aschoff bodies; and a final stage of healing through either resolution or organization with the formation of a scar.

In this rheumatic process the connective tissue of all the structures of the heart—endocardium and valves, myocardium, pericardium, and coronary vessels—is involved with varying intensity. It will be more convenient to describe the changes in the endocardium and valves in conjunction with the individual valvular lesions (pages 463 and 489). In the following, we will first discuss the development of rheumatic inflammation in the myocardium, the site in which it was first studied in detail. But it is to be reiterated that the process is essentially the same in other parts of the body.

The characteristic and specific lesions of the myocardium develop in the interstitial connective tissue Opportunities to study the uncomplicated initial phases are not common, for death is rare in the first two weeks of rheumatic infection. The first changes consist in swelling of the collagen fibers and exudation of fluid and cells Gross and Ehrlich[28] incline to the opinion that the changes in the collagen fibers are the primary phenomenon. The swollen collagen fibers merge with one another to form a homogeneous mass that is intensely acidophilic, appearing bright red in the hematoxylin-eosin preparation, and takes fibrin stains. Because of the latter property the process has been termed fibrinoid degeneration, but Gross and Sacks,[31] who have studied the matter in detail, find practically no fibrin at this or subsequent stages of the evolution of the Aschoff body. The swelling of the fibers is generally regarded as a manifestation of necrosis of the collagen. Klinge has found by means of silver stains that, while the collagen reactions are absent, the skeleton of the component fibrils is intact and stains like reticulum fiber, although it is masked by swelling of the ground substance. However, Gross[31] has found that there is actual breaking up of the fibers, *i e.*, true necrosis. The changes in the connective-tissue framework are accompanied by exudation of fluid, resulting in small areas of edema, round cells, and sometimes polymorphonuclear leukocytes; the cellular exudation is rarely conspicuous in the early phases

The Aschoff Body.—By the end of the second week, according to Gross and Ehrlich and Klinge, proliferation of the fixed connective-tissue cells starts This proliferation results in the granulomata which constitute the chief histological characteristic of the rheumatic inflammatory process. They are known after their dis-

coverer as Aschoff bodies or, because of their size, as submiliary nodules; individual fresh Aschoff bodies without surrounding changes are not visible to the naked eye. While it has been claimed by Clawson[14] and others that the Aschoff body is not absolutely specific for rheumatic infection and may be found in scarlet fever and subacute bacterial endocarditis, the recent studies of Gross are strongly in favor of their specificity.

The Aschoff body most often develops in the adventitia of a small artery or vein; this was the case in 44 of 49 submiliary nodules which McEwen[57] studied in serial sections The Aschoff body

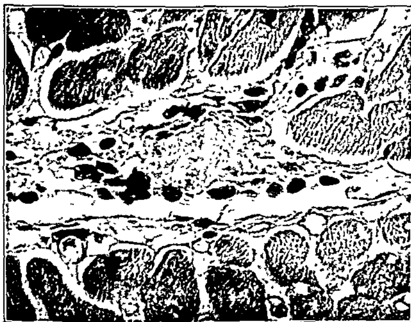


FIG 3—The life cycle of the Aschoff body I Central area of collagen necrosis with beginning surrounding proliferation of histiocytes ("Aschoff cells")

varies in appearance with the stage of its development, Gross and Ehrlich have found correlations between the morphology of the lesion and the phase of the rheumatic infection At the height of its development, a typical Aschoff body consists in cells surrounding or embedded in a matrix of the homogeneous eosinophilic substance described above as derived from swollen and necrotic collagen fibers; the appearance sometimes simulates that of a Langhans tubercle The characteristic cellular element (Aschoff cell) varies in size from a little larger than a lymphocyte to a true giant cell The larger elements have ill-defined borders and frequently long cytoplasmic

extensions These cells are often multinuclear and may form large, irregularly outlined syncytial masses. The nuclei may have a wheel-spoke arrangement like that of a plasma cell. The cytoplasm is basophilic, staining red with methyl pyronin The origin of these large cells has given rise to considerable controversy, different investigators have derived them from lymphocytes or monocytes of the circulating blood, vascular endothelium, or the histiocytes or fibroblasts of connective tissue Gross and Ehrlich believe that "it is safest to assume that they arise from *mesenchymal ele-*



Fig 4 The life cycle of the Aschoff body II Large histiocytes proliferate throughout the necrotic collagen

ments, understanding by this term an ultimate derivation from the mesenchyme which may or may not have passed through a differentiation into mature cell types such as lymphocytes, histiocytes or fibroblasts " It seems that these cells may act as scavengers for the products of collagen necrosis In addition to the cells just described, a varying number of lymphocytes, polymorphonuclear leukocytes, plasma cells, and fibroblasts may be present

About the ninth to the sixteenth week after the onset of the causative rheumatic exacerbation, according to Gross and Ehrlich, the regression and transformation of the Aschoff body into a scar

begins The cells are replaced by fibroblasts and the ultimate result is a connective-tissue scar. Myocardial scars of rheumatic origin are often perivascular

Aschoff bodies can be demonstrated in the heart in a very high proportion of cases of active rheumatic infection Thayer[88] found them in 93.7 per cent of his cases. In patients who succumbed during the first attack of rheumatic fever, Gross and Ehrlich found Aschoff bodies in almost 100 per cent of cases, in over 90 per cent of other cases of active rheumatic infection, and in over 64 per cent

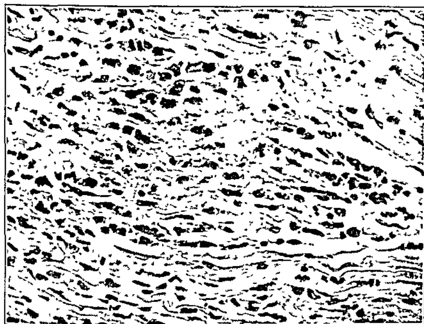
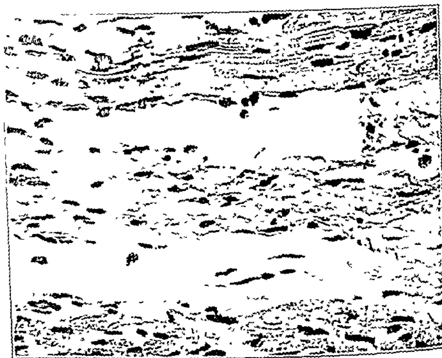


Fig 5 —The life cycle of the Aschoff body III Beginning fibroblastic activity and organization of the nodule

of cases of rheumatic heart disease in which death resulted from cardiac failure without clinical evidence of active infection at the end The left ventricle and interventricular septum seem to be the sites of predilection for Aschoff bodies In their cases dying in the first attack of rheumatic infection Gross and Ehrlich found Aschoff bodies in the interventricular septum and posterior wall of the left ventricle almost invariably, while these lesions were present in the left auricle, left posterior papillary muscle, and pulmonary conus of the right ventricle in about 60 per cent. Submiliary nodules are generally more numerous in the subendocardial portions

[illegible] Coombs found that they have no special [illegible] the conduction system.

[illegible] The most important point in relation to [illegible] about which histology tells us least, namely, [illegible] muscle fibers. In active rheumatic infection the [illegible] immediately adjacent to the Aschoff bodies [illegible] exhibit severe regressive changes. There [illegible] of myomalacia not in evident relation to [illegible] some of these are evidently secondary to arterial [illegible] from rare exceptions these changes are so cir-



[illegible] of the Aschoff body. IV. Conversion into scar [illegible]

cumscribed as to be of little significance for the genesis of heart failure. The ventricular muscle in general may show cloudy swelling and fatty change, but these are rarely severe, differ in no wise from the common findings in other infectious diseases, and scarcely indicate severe damage to the heart muscle. In the left auricle on the other hand the rheumatic inflammation, instead of being confined to circumscribed granulomata as in the ventricles, may be quite diffuse and the muscle fibers severely damaged. Indeed, in cases of mitral stenosis with great dilatation of the left auricle the myocardium of this chamber may be practically destroyed; this is

perhaps attributable to the effects of both the high tension and the inflammatory lesion. The significance of the high intra-auricular tension is indicated by the absence or far smaller extent of the changes in the right auricle. The auricular changes are further discussed on page 493.

The Coronary Arteries.—While it has long been known that rheumatic infection may produce lesions of the coronary arteries, the frequency and severity of the latter have become evident only in recent years. Investigations by Karsner and Bayless[42] and Gross, Kugel and Epstein[29] have shown that the coronary arteries are regularly implicated in rheumatic heart disease, although the severity of the changes and the number of branches involved varies. In patients succumbing during active rheumatic infection, some of the coronary branches generally reveal arteritis, characterized by such changes as cellular infiltration, proliferation of fixed cells, edema, eosinophilic swelling of the collagen, necrosis, destruction of the elastic tissue, and thrombosis Most of the changes are not specific for rheumatic infection, but sometimes Aschoff bodies are found. The arteritis may affect coronary branches of all sizes According to L. Gross, Kugel and Epstein,[29] the severe forms of rheumatic arteritis almost always occur under the age of fifteen years H. Gross and Oppenheimer[30] found no evidence in their clinical and necropsy observations that rheumatic infection predisposes to coronary arteriosclerosis of a severity sufficient to be striking at necropsy. On the other hand, detailed histological studies by Karsner and Bayless and L. Gross, Kugel and Epstein have shown that long-standing rheumatic heart disease favors the development of regressive changes in the walls of the coronary arteries In rheumatic heart disease of long duration, the last named investigators found premature sclerosis and thickening of the coronary arteries due to elastic and collagenous hyperplasia; their findings indicate that the victim of chronic rheumatic heart disease has coronary arteries belonging to an age period considerably older than his actual years Thus, L. Gross and his co-workers mention a patient, aged fifteen years, in whom the right circumflex coronary artery had an intima of the thickness usually seen in the fourth decade of life It remains to be determined to what extent the thickening of the coronary arteries in rheumatic heart disease is a manifestation of increased wear and tear due to the greater blood flow required for the hypertrophied heart, and to what extent it is due to organization of the arteritis of the active stages. Probably both factors participate.

Thrombotic occlusion of small coronary branches is a common result of rheumatic arteritis. Nor are mural thrombi of the large branches rare. However, major coronary thrombosis with occlusion of a large branch and the clinical picture of myocardial infarc-

tion is a great rarity. Breitenecker[8] described an instance of such occlusion of the right coronary artery producing sudden death in a young girl, aged twenty-two years, with rheumatic myocarditis and aortitis, and Perry[66] another of thrombosis of the left coronary artery in a boy, aged fourteen years, with rheumatic heart disease who had had angina pectoris. A further case, without necropsy but with the clinical picture and electrocardiographic changes of myocardial infarction, was published by Slater.[77]

The Pericardium.—The pericardium is probably implicated in practically every severe attack of rheumatic carditis, although the lesions may resolve so that they are not found in the patient who succumbs years later after activity has subsided. This is indicated by the following findings of Coombs:[15] Of patients dying in the first decade, 100 per cent had pericardial lesions; in the second, 83.3 per cent, in the third, 41.6 per cent; in the fourth, 23 per cent; and after the age of forty years, 26 per cent. The inflammation of the pericardium results in reddening of the surface, deposition of fibrinous layers on the surface, exudation of fluid into the cavity, and ultimately, if the inflammatory products are not resorbed, the formation of pericardial thickenings and adhesions of the layers to one another and the surrounding structures. Calcification of the pericardium is a rare outcome. Histologically, the lesions are typical of the rheumatic process, and Aschoff bodies are often demonstrable during activity. Large pericardial effusions of rheumatic etiology are unusual, Coombs found effusions of a measurable quantity in only 10 per cent of his rheumatic patients succumbing before the age of sixteen years, and in older individuals they are much rarer. The rôle of pericardial adhesion and effusion in the causation of heart failure is considered in Chapter XXXI.

The Mechanism of Heart Failure in Rheumatic Carditis.—We may now turn to the pathogenesis of the failure of the rheumatic heart, and especially the relation of the latter to the anatomical changes just described.

The proportion of rheumatic cardiacs who still have active carditis at the time of the final failure of the heart varies with the age at which the latter occurs. This is strikingly illustrated by the findings of Rothschild, Kugel and Gross.[7] They examined 161 rheumatic hearts with the following results:

Age at death	Per cent with active carditis
1 to 10	100
11 to 20	95
21 to 30	78
31 to 40	70
41 to 50	39
51 to 60	13
61 to 70	12
71 to 80	0

Similar observations were made by Coombs.

In recent years there has been growing appreciation of the great importance of exacerbation of *active* carditis for the failure of the rheumatic heart. However, the figures just cited show that it is not always concerned, for there are cases of rheumatic heart failure without active carditis. In these, mechanical burdens imposed by the valvular defects—the significance of which has been too much deprecated of recent years, perhaps as a reaction to the overemphasis of the older clinicians—are of fundamental significance. We shall consider these factors in turn

The Rôle of Active Myocarditis in Rheumatic Heart Failure.—From the above figures it appears that when heart failure develops in young rheumatic individuals the rôle of active carditis, which almost always includes active myocarditis, must be taken into account. This is also indicated by the clinical course and the anatomical findings. Especially in children and young adults, one often finds that the appearance of symptoms of decompensation follows fever or other evidences of exacerbation of the rheumatic infection and that with the subsidence of the infection the circulation improves. Furthermore, at the necropsy of such patients the valvular defects may not be severe, sometimes mechanically insignificant, but the activity of the inflammatory process is pronounced. While there thus seems no doubt that the lighting up of the rheumatic infection is responsible for heart failure in these cases, the nature of the connection—apart from the rare cases with extremely widespread degeneration and destruction of the heart muscle—is not clear. In many instances, despite a considerable number of Aschoff bodies and other changes in the connective-tissue framework, the heart muscle reveals comparatively little histologically demonstrable change, not more than is often seen in other infections without heart failure One is driven to the assumption—though it is no more than an assumption—that rheumatic infection damages the heart muscle and lowers its functional capacity in some way that is not reflected in histological changes evident to present methods of investigation.

In addition to the development of heart failure, an indication of damage to the myocardium in active rheumatic infection is afforded by the great frequency of *electrocardiographic changes* in acute rheumatic fever, even though there are neither symptoms nor physical signs of cardiac implication. By making frequent tracings, Swift and Cohn[88] found electrocardiographic changes in 35 of 37 cases of acute rheumatic fever. Rothschild, Sacks and Libman[73] found abnormalities in the electrocardiograms of 61 of 65 patients with acute rheumatic fever It is to be emphasized that such high incidences are obtained only by taking repeated electrocardiograms, for the changes are usually evanescent and vary from day to day The most frequent findings are prolongation of the *P–R* interval

and alteration in the form of the *Q-R-S* complex, the *S-T* segment and the *T* wave. Such disturbances in cardiac mechanism as premature contractions, auricular fibrillation or flutter, auricular or ventricular tachycardia, nodal rhythm, or auriculo-ventricular, bundle-branch or sino-auricular block may occur (Parkinson, Gosse and Gunson[65]) In fact, practically all the electrocardiographic aberrations occurring in coronary arteriosclerosis and thrombosis *have been observed in rheumatic fever, including the sequence of* elevation of the *S-T* segment followed by inversion of the *T* wave which is so common in coronary thrombosis. Most of the changes also occur, although much less often, in other acute infections (page 664) The ephemeral nature of most of the electrocardiographic abnormalities in rheumatic fever indicates that they are due to reversible changes in the myocardium But occasionally permanent defect of auriculo-ventricular conduction or other changes *remain, doubtless the results of the formation of* an appropriately located scar in the heart muscle

Significance of the Mechanical Burdens Imposed by Valvular Defects in the Failure of the Rheumatic Heart—In older patients *with long*-standing valvular defects, contrary to the cases just considered, heart failure is most often not due to exacerbation of the rheumatic inflammatory process.* Very often there is no history of rheumatic fever or chorea and even careful questioning elicits no anamnesis of the rheumatic infection that undoubtedly existed many years before. They may have no fever, arthritis, anemia, acceleration of the rate of sedimentation of the red cells, or other indication of *rheumatic activity And at necropsy there is either* complete absence of active inflammatory lesions of the heart, or the few Aschoff bodies and other evidences of myocarditis are so scattered that they scarcely bespeak significant activity. The valvular defects are severe and there is pronounced dilatation and hypertrophy, which indicates that the heart has performed increased work for a long time The causes of heart failure in these cases are probably fundamentally the same as those which lead to ultimate fatigue and failure in all forms of cardiac hypertrophy, *e g.*, in hypertension. What is known about the genesis of this form of heart failure has been discussed above, where it is pointed out *that inadequacy of the metabolic exchanges of the hypertrophied* muscle with the blood is probably of great significance. For example, in aortic valvular lesions acquired in early life, as the valvular deformity becomes more pronounced through shrinking of scar tissue and secondary atherosclerosis (page 466), more and more hypertrophy of the left ventricle develops, until the muscle

* However, it must not be forgotten that even initial attacks of rheumatic infection may occur after the age of sixty years, Ferris and Myers[44] have published such cases with death from heart failure, and I have encountered them

mass "outgrows" its blood supply. The accommodation of the blood supply to the hypertrophy of the left ventricle is hampered by the premature sclerosis of the coronary arteries which is an almost inevitable accompaniment of rheumatic heart disease (page 345). Even though this sclerosis does not strikingly narrow the coronary lumens, it may well interfere with *increase* in blood supply and vasomotor adaptation necessary to meet the greater blood flow needed by the overworked and hypertrophied left ventricle. Moreover, the functional capacity of the heart muscle is doubtless often diminished because of the changes incidental to advancing years and perhaps also because of residual damage from the myocarditis that existed years earlier. In mitral stenosis, failure is often precipitated by the onset of auricular fibrillation (page 513), in the causation of which the mechanical factor of auricular distention is perhaps concerned And in other instances pericardial thickening and adhesions may play a part, if only an accessory one, in overburdening the heart.

In many cases the two mechanisms just described are both concerned in the causation of the failure. Following a rheumatic infection, the patient remains with a valvular defect, which is well compensated. But a fresh exacerbation is accompanied by decompensation, and at necropsy one finds not only the valvular defects and hypertrophy emanating from the old infection but also fresh carditis Very often, the final failure occurs only after a number of attacks of decompensation, each due to lighting up of the rheumatic infection.

Subacute Bacterial Endocarditis.—Libman[51] long ago pointed out *that subacute bacterial endocarditis almost always develops in* individuals with well-compensated valvular defects or congenital anomalies; only rarely does this form of endocarditis complicate pronounced heart failure. Libman's observation is of practical importance, for while subacute bacterial endocarditis should be among the first thoughts when fever or embolic phenomena appear in a well-compensated cardiac patient, this explanation is far less likely in the presence of severe heart failure. Moreover, while Buchbinder and Saphir[9] found chronic passive congestion of the organs in each of 40 necropsies, most victims of active subacute bacterial endocarditis do not develop heart failure until the terminal stages of the disease. The same is not true of *Libman's*[51] *bacteria-free* stage of the disease, in which heart failure may play a prominent part. Libman[52] further pointed out, what is likewise often a diagnostic aid, that subacute bacterial endocarditis rarely develops in the presence of auricular fibrillation or flutter, and that these arrhythmias are extremely infrequent in the active stage of the disease. Thus, Rothschild, Sacks and Libman encountered auricular fibrillation in only 1 of 100 active cases of subacute bacterial

endocarditis, and in this instance it appeared three days before death. On the other hand, of 14 patients in the bacteria-free stage 3 had auricular fibrillation and 1 flutter. Moreover, in 200 individuals with auricular fibrillation observed by Rothschild, Sacks and Libman for one to ten years, none developed subacute bacterial endocarditis.

The reason why subacute bacterial endocarditis so rarely appears in patients with pronounced heart failure or auricular fibrillation does not seem to have been elucidated

The fact that most patients with active subacute bacterial endocarditis do not develop heart failure other than terminally indicates that the myocardium does not suffer severely. This is rather peculiar in the light of Buchbinder and Saphir's observation of extensive myocardial lesions (minute emboli, infarcts and abscesses, Aschoff bodies and perivascular fibrosis) in all their cases. Apparently these are of slight functional significance, for Rothschild, Sacks and Libman found little alteration in the ventricular complexes of the electrocardiogram, although prolongation of the *P–R* interval was present in 10 of 61 cases.

Abnormal Rhythm.—A change in the rate or rhythm of beat may so diminish the accomplishment of the heart that cardiac failure results Exceptionally, the change in rhythm or rate *per se* causes heart failure, and with reversion to the normal sequence of beat the circulation returns to normal This is seen especially in paroxysmal tachycardia. Much more often, the precipitation of cardiac failure by arrhythmia occurs in a heart already the seat of manifest disease, and the change in rate or rhythm is only one of the factors leading to cardiac insufficiency. In this respect, fibrillation of the auricles is by far the most important of the disorders of the heart beat, although other disturbances of rate or rhythm may have the same effect.

Auricular Fibrillation.—There is ample clinical evidence that auricular fibrillation lessens the functional capacity of the heart. One often encounters individuals with mitral stenosis or other diseases of the heart who are well compensated until the auricles begin to fibrillate; then, manifestations of heart failure quickly appear. It is true that there are also instances in which auricular fibrillation, especially when well controlled by digitalis, is compatible with a fairly active life. But such patients can rarely carry out as vigorous exercise as when the rhythm was regular. In paroxysmal auricular fibrillation the only subjective complaints may be of palpitation, due to the rapid and irregular beat, and not of the consequences of heart failure. However, with rapid ventricular rates there can be little doubt that during the episodes the functional capacity of the heart is diminished.

The evidence is unequivocal that auricular fibrillation tends to

decrease cardiac output. In the experimental animal, Stewart[82] and his associates have shown that rapid auricular fibrillation diminishes the output of the heart. The first measurement of cardiac output in human fibrillation was made by Lundsgaard, who found in one subject that the minute volume was less than when the rhythm was regular. Smith, Walker and Alt[79] found in 3 patients with auricular fibrillation that the restoration of normal rhythm with quinidine was followed in 2 instances by increase in cardiac output of 29 and 31 per cent, respectively, while the third showed no change Kerkhof[44] studied the cardiac output by the acetylene method in 9 patients with mitral stenosis before and after the restoration of normal rhythm by means of quinidine, the minute volume averaged 25 per cent more when normal rhythm was present Harrison[35] and his associates found the cardiac output in heart failure about the same whether or not auricular fibrillation was present, but in the absence of failure the output was somewhat less in fibrillators than in those with normal rhythm The detailed studies of Stewart[83] and his collaborators showed that when a patient with auricular fibrillation returns to sinus rhythm the cardiac output per stroke and minute, the work of the heart, and the velocity of blood flow all increase; the reverse changes occur with change from sinus rhythm to auricular fibrillation.

Fibrillation of the auricles adversely affects the functional capacity and lowers the output of the heart in several ways:

1. When the conductivity of the bundle of His is unimpaired, the ventricular rate is rapid. This abbreviates the diastolic rest period and predisposes to myocardial fatigue, especially if the muscle is diseased or the ventricles are forced to perform added work because of hypertension or a valvular defect

2. The ventricular rate may be sufficiently rapid to impede adequate diastolic filling of the ventricles.

3. Impulses are transmitted along the bundle of His at irregular intervals. Some ventricular systoles are thus evoked so soon after the preceding contraction that the filling of the ventricle is small and its contractility not yet fully restored. The result is that the systole does not open the aortic valve or does so but feebly and a pulse deficit results A large pulse deficit is usually accompanied by severe heart failure.

4. The fibrillating auricle propels practically no blood, with the result that the quota of ventricular filling due to auricular systole is lost. Experiments by Lewis,[50] Hirschfelder,[40] Gesell,[25] Wiggers and Katz,[92] and others indicate that normally auricular systole is probably responsible for about 20 to 35 per cent of the total ventricular filling However, the importance of auricular contraction doubtless varies greatly with the conditions, and appears to be

especially significant when there is tachycardia, functional impairment of the ventricles, or mitral stenosis:

(*a*) If the heart rate is slow, diastole is long enough to allow relatively complete ventricular filling by the venous pressure. On the other hand, when diastole is shortened in tachycardia, auricular contraction would seem to be more needed for the filling of the ventricle.

(*b*) As pointed out by Gesell, auricular systole increases the efficiency of the ventricle not only by the augmented filling as such but also by heightening the initial tension and augmenting the initial length of the muscle fibers, the result of which, according to Starling's law of the heart, is more powerful ventricular contraction. This factor is probably especially important when the ventricle is diseased, for a functionally impaired ventricle requires a larger diastolic filling to perform the same amount of work

(*c*) In mitral stenosis, ventricular filling is hampered by the increased resistance to flow, which renders the aid of auricular contraction all the more necessary for the filling of the ventricle That the auricle does perform more work in mitral stenosis is shown by its hypertrophy, and its functional elimination is correspondingly more important

5 In addition to favoring the appearance of heart failure, another deleterious consequence of auricular fibrillation is that it promotes the formation of auricular thrombi, which may embolize (page 520).

There can be no doubt that, in most cases at least, by far the more important elements in the genesis of heart failure precipitated by auricular fibrillation are those due to the rapid and irregular action of the ventricles, and not the loss of the motor power of auricular systole This is shown by the great improvement that takes place, despite the persistence of fibrillation of the auricles, when digitalis slows the ventricle. It is when the ventricular rate is very rapid, above 130 per minute, that heart failure is most severe. Contrariwise, these cases of auricular fibrillation with a relatively slow ventricular rate due to impairment of auriculo-ventricular conduction, usually seen in elderly arteriosclerotic individuals, often have comparatively few symptoms of heart failure.

The clinical manifestations of heart failure precipitated by auricular fibrillation will be considered in conjunction with the underlying diseases. Here it may be remarked that the pattern of heart failure evoked by auricular fibrillation is greatly affected by the conditions under which it occurs. Thus, in mitral stenosis without previous pronounced heart failure auricular fibrillation may produce intense pulmonary engorgement with little systemic venous engorgement; evidently, the effects of the fibrillation and the obstruction at the mitral orifice are summated in the pulmonary engorgement. Contrariwise, in patients with mitral stenosis and

marked pulmonary engorgement, the onset of auricular fibrillation may so diminish the functional capacity of the right ventricle that the tension in the pulmonary circuit falls and dyspnea and orthopnea lessen *pari passu* with increase in systemic venous engorgement. *The onset of auricular fibrillation, especially the paroxysmal form,* is sometimes accompanied by faintness and other manifestations of cerebral ischemia.

Other Arrhythmias.—*Premature contractions* are rarely significant for the functional accomplishment of the otherwise unimpaired heart. This is especially true because when the heart is strained by exercise the resulting acceleration in rate usually is accompanied by disappearance of the extrasystoles Such symptoms as premature contractions occasion in those without heart failure are usually evident only in hyperesthetic individuals, and consist in consciousness of the extrasystole, the compensatory pause, or the ensuing strong systole with its large arterial wave Rarely, a run of extrasystoles or an unusually long compensatory pause produces faintness from cerebral ischemia (page 282). On the other hand, when the heart is functionally impaired, it would seem that frequent premature contractions, especially of ventricular origin, may prove a serious added burden Premature contractions which do not open the semilunar valves result in expenditure of cardiac energy without corresponding accomplishment, which, when often enough repeated, is doubtless a significant contribution to myocardial fatigue in an already strained heart. Wenckebach and Winterberg[90] have observed that during runs of ventricular extrasystoles the cervical veins may become distended and the auricles dilated (seen fluoroscopically).

The effect of *auricular flutter* on the circulation is largely dependent on the ventricular rate. If the ventricle responds to every third or fourth auricular beat, so that the ventricular rate is little or not at all accelerated, symptoms of heart failure may be evoked by only considerable exertion. When the ventricle responds to every second auricular contraction and has a rate of about 130 to 160 per minute, the functional capacity of the heart is greatly diminished and severe failure may develop, especially in those with pre-existent limitation of cardiac reserve Stewart[83] and his associates found that auricular flutter is accompanied by decrease in cardiac output per beat and per minute. In addition to symptoms emanating from pulmonary and systemic venous engorgement, there may be protracted mental torpor and Cheyne-Stokes breathing, evidently due to deficiency in cerebral blood flow. There are also instances of auricular flutter in which the ventricular rate is of the order of 140 per minute for weeks and even months and yet the symptoms are only palpitation, weakness, faintness, and vertigo, with dyspnea present only on unwonted exertion. In paroxysmal

flutter, the symptoms are akin to those of paroxysmal tachycardia (page 612) and may consist in merely episodes of faintness or vertigo. In the rare paroxysms of auricular flutter in which the ventricle responds to every auricular contraction and thus has a rate of 240 or more per minute, the patient may fall unconscious or have an epileptiform convulsion.

Ventricular fibrillation is an arrhythmia inconsistent with the maintenance of significant cardiac output; the result is that the circulation ceases with consequent loss of consciousness and disappearance of the pulses Well-established instances of ventricular fibrillation with survival are those recorded by Kerr and Bender[45] and Schwartz and Jezer[75] in complete heart block (page 280). Ventricular fibrillation may occur in the dying heart though apparently it is not the rule. Electrocardiographically, Robinson[69] detected ventricular fibrillation in 2 of 7 persons dying of acute infections, although in 1 the rhythm again became regular before the end Halsey[32] obtained the typical electrocardiogram of ventricular fibrillation in an individual dying of pneumonia. MacWilliam[58] long ago suggested that sudden death in angina pectoris and other forms of heart disease is due to ventricular fibrillation In coronary thrombosis, at least, this would seem very probable, for experimental occlusion of a large coronary trunk may lead, following periods of multiple ventricular extrasystoles and ventricular tachycardia, to ventricular fibrillation Smith[73] was recently able to demonstrate electrocardiographically that ventricular fibrillation preceded sudden death in a patient who had suffered myocardial infarction a few hours previously. Ventricular fibrillation probably is concerned in death from electrocution. Experimental findings indicate that sudden death following the administration of chloroform, digitalis, strophanthin, quinidine, or epinephrin may sometimes result from ventricular fibrillation. Sudden death due to fright has also been attributed to ventricular fibrillation, but this is merely a hypothesis.

Paroxysmal tachycardia and *heart block* are considered in Chapter XVII.

Overexertion.—Overexertion was formerly highly esteemed as a cause of heart failure. Almost always, however, this occurs in individuals with previously diseased hearts, and even then is probably not nearly as common as was thought.

Exercise.—Exercise increases the work of the heart through augmentation of both factors—the cardiac output and the average aortic pressure—which determine the cardiac load. Christensen[11] has shown that during violent exercise trained athletes can increase the cardiac output to as much as 900 per cent of the resting value. During vigorous exercise the systolic pressure rises above 180 mm. of mercury with little change in diastolic pressure, although the

latter sometimes falls. (Unpublished observations by Dr. E. Z Epstein and the writer.) The trained athlete can thus increase the work of the heart by the order of 1200 per cent While the untrained individual cannot attain such height, nevertheless he can augment cardiac work five or more times.

Pari passu with the increase in cardiac work due to exercise, the diastolic rest period is diminished by tachycardia

The combination of more work and less rest would seem ideal for the provocation of heart failure. Nevertheless, it is extremely rare, if it occurs at all, that the previously healthy heart should fail as a result of overexertion. A few cases are recorded in which such a consequence of events seems probable Perhaps the most striking are two personal experiences of Allbutt,[2] following an Alpine climb and running after a train he became dyspneic and remained incapable of much exercise for a time On each occasion he was able to demonstrate dilatation of the right heart by percussion Perhaps the reason that overexertion so rarely leads to failure of the healthy heart is that the limits of exercise are not determined by the heart alone but rather that "the sum of the changes taking place throughout the body brings about the final cessation of effort" (Bainbridge[4]) Apparently, exercise is stopped by other limiting factors before the healthy heart is overstrained The limitations imposed by the inextensible pericardium probably serve to prevent acute and pronounced overdistention and consequent failure (page 303)

In the vast majority of instances, including all that I have seen, in which heart failure followed great physical effort, examination and subsequent observation reveal that the heart was previously diseased. In individuals with heart disease, either the initial decompensation or intensification of pre-existent heart failure occasionally follows such overexertion as running after a street car or lifting a heavy weight This seems to be more apt to occur in persons with coronary arteriosclerosis than in those with valvular defects. In arteriosclerotic, hypertensive, or syphilitic heart disease, either angina pectoris, or more rarely left ventricular failure with pulmonary edema, or even sudden death, may be precipitated by overexertion. That subjects of coronary arteriosclerosis should be especially susceptible to deleterious effects from overexertion seems readily comprehensible in view of the obstacles that the narrowed coronaries must offer to an increase in the blood supply to the heart commensurate with the greater work, Bainbridge[5] estimates that during severe exercise coronary flow may be seven times greater than during rest. Nevertheless, the number of cases I have seen in which the precipitation of heart failure could be attributed with fair likelihood to overexertion has been small. It should, however, be mentioned that this is not the experience of

all others; Wollheim[84] found that overexertion was concerned in the induction of 61 of 200 instances of cardiac decompensation.

Coitus involves an exertion that is especially apt to lead to acute cardiac failure in those with a diseased, notably arteriosclerotic, heart. Some years ago a woman with mitral stenosis was admitted to Beth Israel Hospital with fulminating pulmonary edema that had followed immediately after coitus; she had had two previous similar episodes In the arteriosclerotic subject, sudden death during or following coitus is not a great rarity. Perhaps one factor in the pathogenesis of such heart failure is the extreme tachycardia; Boas and Goldschmidt[6] found with their cardiotachometer that during intercourse the heart rate may reach 145 per minute.

Clinical experience indicates that continued hard work favors the decompensation of the diseased heart. While statistics on the point are hard to obtain, I have the impression that the compensated stage of valvular and other forms of cardiac strain does not average as long in working people as in those who can afford leisure. Clinical observation also indicates that hard physical labor over many years favors the progress of arteriosclerosis. These deleterious effects of long-continued labor on the heart and arteries are doubtless significant in the explanation of Pearl's finding that length of life tends to vary inversely with the mechanical work performed during the course of life.

Another and much disputed question is whether such athletic activities as competitive rowing, football, etc., which produce cardiac hypertrophy, ultimately lead or predispose to disease of the originally healthy heart—"athletic heart." The problem was studied by Dublin,[19] who investigated the life histories of 5000 college athletes. He found that while 20 per cent of deaths among insured persons after the age of forty-five years are due to heart disease, among athletes in this group 32 per cent succumb to cardiac disease. According to Dublin, this "suggests, even if it does not prove, that indulgence in athletics may in a good many instances have deleterious effects on the heart." But it should be remembered in this connection that most of these deaths after forty-five years are due to coronary arteriosclerosis and thrombosis, a disorder to which those of sthenic bodily habitus are predisposed, and most athletes are of this constitutional type.

Related Causes of Cardiac Strain.—Pregnancy, obesity, overeating, overdrinking, and surgical operations may burden the heart in ways that are related to the effects of physical exercise, and thereby precipitate failure of the diseased heart. In order to avoid repetition, these factors will be considered in the sections on Treatment.

Relations of the Blood Volume to Heart Failure.—*Increase in circulating blood volume* has been considered as a cause of heart failure (page 73) It is true that in most instances of heart failure

the circulating blood volume is increased. However, there is good reason to believe that the increase in circulating blood volume is a *consequence* and not a *cause* of heart failure (page 72), although it may in turn evoke symptoms through augmenting passive engorgement of the lungs or other parts.

The example of polycythemia vera shows that the circulating blood volume may be enormously increased without enhancing the work of the heart to a significant extent. In this disease the circulating blood volume may be double the normal for many years without resulting in cardiac hypertrophy (See Harrop[17] for literature.) The latter would doubtless appear if cardiac work were notably augmented over so long a period What is perhaps surprising is that the greatly increased viscosity of the blood is not more significant for the dynamics of the circulation Viscosity affects circulatory dynamics through increasing peripheral resistance. The absence of high blood pressure in many of the cases thus shows that the augmented viscosity has had little effect on blood flow. The explanation perhaps is afforded by axial flow of the corpuscles in the small vessels, only a layer of plasma comes in contact with the vessel wall, so that peripheral resistance is not increased as much as might be presupposed When heart failure develops in polycythemia, as it often does in long-standing cases, it results from hypertension or coronary arteriosclerosis and thrombosis, which are common complications.

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CHAPTER XX

ENLARGEMENT OF THE HEART

The size of a chamber of the heart is largely determined by the ratio of its functional capacity to the work which it is called upon to perform. If the latter is diminished, the chamber tends to atrophy. The outstanding clinical example is the atrophied left ventricle in relatively pure mitral stenosis dating back to early life. Far more common and important, however, is the contrary displacement of the ratio between functional capacity and work demanded, namely, that in which the former is decreased relative to the load. In either event, there spring into play mechanisms (Chapter XVIII) which tend to restore the original equilibrium between functional capacity and work called for. Among these mechanisms are dilatation and hypertrophy of the heart, which constitute the substrata of cardiac enlargement.

The evidence establishing the compensatory function of cardiac hypertrophy and dilatation is reviewed in Chapter XVIII. There are cited the experiments of Starling and his followers showing that in the heart-lung preparation, (1) There is a direct linear relationship between the work and the diastolic volume of the heart, and (2) the size of the heart tends to vary inversely with its functional capacity.

That the principles shown by Starling to govern the size of the heart of the experimental animal also apply in human pathology would seem, both *a priori* and in the light of the evidence discussed in Chapter XVIII, very probable. Starr, Collins and Wood[19] have adduced quantitative support of the conception. In 50 subjects, both healthy and with hypertension, valvular defects and other forms of cardiac strain, they measured the area of the cardiac silhouette and calculated the work of the left ventricle from the product of the average arterial pressure and the cardiac output determined by an improved ethyl iodide method. Starr and his associates found that when the size of the heart was plotted against the work performed, there was a fairly close linear relationship for the normals and the cardiac patients without heart failure. On the other hand, this linear relationship did not hold for those cases in which heart failure threatened; then, the heart was disproportionately large in comparison to the work performed.

Clinical Interpretation of Cardiac Enlargement.—In the light of the foregoing, it would seem that to the clinician *enlargement of the heart indicates that the organ is laboring under difficulties due to a relative increase in the ratio of load to functional capacity and is*

tending to overcome the consequent embarrassment by the compensatory mechanisms of dilatation and hypertrophy

Since enlargement of the heart is merely the expression of compensatory mechanisms, it will be clear why *there is no strict proportionality between the extent of the enlargement and the peripheral evidences of heart failure.* Thus, one not rarely encounters large hearts in patients with aortic regurgitation or hypertension who are able to perform hard work with little handicap Nevertheless, marked enlargement of the heart is of unfavorable prognostic significance. This is because hypertrophy *per se* causes little enlargement of the heart so that any considerable increase in the size of the cardiac silhouette bespeaks notable dilatation, and dilatation is but a precarious compensatory mechanism always liable to give way. Of especially bad prognostic omen is progressive enlargement of the heart, which shows that the disproportion between functional capacity and load has not been entirely remedied by the existing degree of enlargement so that further dilatation is called for, a compensatory mechanism which sooner or later reaches its limit (page 303) On the other hand, decrease in size of the enlarged heart is a favorable harbinger, revealing that less dilatation is necessary to meet the load Such regression of dilatation may be due to lessening of the load, as following recovery from acute glomerulonephritis with hypertension Or it may be the result of improvement in the functional capacity of the myocardium, as illustrated in recovery from post-diphtheritic heart disease, where the diminution in the size of the heart may be striking In children there may be considerable diminution in the size of the heart following bouts of rheumatic fever Here, in addition to improvement in the functional capacity of the myocardium, there is probably substitution of hypertrophy for dilatation Marked decrease in cardiac size is seen in the myxedema heart following the administration of thyroid (page 592) Diminution in cardiac size following digitalization is discussed on page 697 Despite these examples, and others that could be cited, it is worthy of emphasis that definitely demonstrable decrease in the size of the enlarged heart is unusual. One must be careful not to confuse changes in the area of the cardiac silhouette due to variations in the height of the diaphragm or other alterations in the position of the heart with actual changes in cardiac size.

Cardiac failure of any considerable (more than a few days) duration is practically invariably accompanied by more or less cardiac enlargement, although this may be difficult to demonstrate clinically because of the notable variations in the size of the healthy heart However, I have never failed to observe at postmortem enlargement of one or more chambers of the heart when there was definite evidence of heart failure (other than agonal) during life.

Indeed, even very brief cardiac failure may result in considerable dilatation of the heart It is true that in some patients with coronary arteriosclerosis or syphilitic aortitis who succumb to coronary thrombosis or narrowing of the mouths of the coronary arteries, dilatation and hypertrophy may be absent. But in such cases the symptoms are not due to motor insufficiency of the heart but were "anginal" manifestations presumably resulting from ischemia of the heart muscle, such symptoms may at times so closely simulate the dyspnea of heart failure as to be practically indistinguishable.

CLINICAL RECOGNITION OF CARDIAC ENLARGEMENT

The clinician is concerned not only with the recognition of cardiac enlargement but also in establishing which chamber or chambers are involved It is also important to determine, so far as feasible, the extent to which hypertrophy and dilatation participate in the enlargement Evidence regarding these points is afforded by both the physical and the roentgenological examinations, which should complement one another and therefore will be considered together. In some instances, the determination of the electrical axis and certain other features of the electrocardiogram afford valuable information regarding the chamber involved.

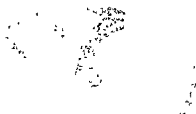
It cannot be emphasized too strongly that adequate interpretation of cardiac enlargement rests on the determination of the contribution of the individual chambers to the augmentation in the volume of the heart There should be a "chamber by chamber" analysis of the heart For this reason, the manifestations of enlargement of the single chambers of the heart will be considered successively in the following For a splendid exposition of the roentgenographic and electrocardiographic changes correlated with the individual forms of cardiac enlargement, the reader is referred to Master's[11] recent monograph Details regarding all aspects of the roentgenology of the heart are authoritatively presented in Roesler's[16] comprehensive survey

The Left Ventricle.—The investigations of Kirch (Chapter XVIII) showed that *hypertrophy* of the left ventricle secondary to hypertension or aortic valvular defects begins in the outflow tract, *i e.*, that portion of the chamber which extends from the apex to the aortic orifice These studies revealed further that at the very beginning not even the entire outflow tract is involved; hypertrophy is initiated in the terminal portion of the outflow tract under the aortic valve and only subsequently reaches the apical portion of the tract. Still later, the hypertrophy extends to the inflow tract, the extending from the apex to the mitral valve. These anatomical *heart* gs elucidate the long-known fact that the early stages of *relative* ophy of the left ventricle cause no demonstrable enlargement

of the heart. For the terminal portion of the outflow tract adjacent to the aortic orifice does not reach the borders of the heart as determined by percussion or radiographic examination with the usual dorso-ventral illumination, and is also difficult to outline clearly by radiography in the oblique or lateral positions Quite commonly, therefore, one is unable to demonstrate enlargement of the heart in individuals with asymptomatic essential hypertension or aortic valvular disease of some years standing, despite the facts that left axis deviation is present in the electrocardiogram and *postmortem experience teaches that such persons invariably* exhibit at postmortem hypertrophy of at least the outflow tract in the left ventricle

Only when the hypertrophy has become more massive and involves the entire length of the outflow tract down to the apex and the apical portion of the inflow tract do the first clinically demonstrable evidences of cardiac enlargement appear, and even then they may be uncertain As a result of the hypertrophy of the apical portion of the heart, there is often a rounding of the apex and an increase in the outward convexity of the lower portion of the left border of the heart which may be very characteristic in the fluoroscope or roentgenogram The rounding is generally best visualized during inspiration when the descent of the diaphragm exposes to view a longer arc of, or the complete, left border One of the results of the rounding of the left border is that the left-most point of the border is situated much higher on the left ventricular arc than normally. At this stage of the process, in addition to rounding of the left border, elongation of the left ventricle is often definitely demonstrable on fluoroscopic examination I do not know whether elongation of the left ventricle due almost entirely to hypertrophy is ever considerable enough to be demonstrable by physical examination as a result of downward displacement of the apex beat to the sixth interspace, but do not recall any instance in which this was definite. It seems doubtful that hypertrophy of the left ventricle is ever massive enough to cause, *per se*, sufficient increase in the transverse diameter of the heart to be definitely recognizable as abnormal When the heart is broadened beyond cavil, considerable dilatation is present.

A physical sign that may reveal hypertrophy of the left ventricle before enlargement is unequivocally demonstrable is the *heaving apex beat.* A heaving apex beat is one that imparts to the palpating finger the sensation of being lifted by a considerable force and "feels hard" Such a heaving apex beat seems to be practically characteristic of left ventricular hypertrophy and is not to be confused with a merely conspicuous apex beat of large amplitude or wide extent. The latter is encountered in overacting or dilated hearts, or may be merely a consequence of an unusually thin chest



during life showed no enlargement. The first roentgenological evidences of dilatation of the left ventricle consist in elongation of the chamber before the broadening is considerable enough to be unequivocally demonstrable With more marked dilatation, the apex beat moves downward to the sixth or even the seventh interspace and outward beyond the normal limit of about 10 cm from the mid-line, in extreme instances, it may pass the anterior axillary



FIG 8 —Hypertrophy and dilatation of the left ventricle, lesser enlargement of the right ventricle, pulmonary engorgement Patient with essential hypertension

line. In such cases, roentgenographic examination with dorsoventral illumination reveals that the left ventricle has a markedly rounded left border, with the result that the chamber appears like an obliquely placed egg, the long diameter extending from the midline downward and outward. The elongated ventricle may reach so far into the diaphragmatic shadow that the egg-like shape and rounding of the left border are apparent only during deep inspiration Examination in the left anterior oblique diameter (left

shoulder to the screen) reveals a marked bulging of the lower portion of the posterior surface of the left ventricle into the retrocardiac space, so that it reaches or passes well over the vertebral shadow; this posterior enlargement may be demonstrable with but moderate dilatation. According to the anatomical studies of Kirch (page 298), the form of the enlargement of the dilated left ventricle may afford information as to the nature of the dilatation. He found that in "tonogenic" dilatation due to increase in the work of the left ventricle (*e. g.*, hypertension, aortic insufficiency), the dilatation consists predominantly of elongation. On the other hand, in "myogenic" dilatation due primarily to myocardial damage (*e. g.*, myocarditis, arteriosclerotic myomalacia), the dilatation is dominated by broadening. These anatomical findings would seem, in general, to be borne out by roentgenologic observations.

In hypertrophy and dilatation of the left ventricle secondary to *mitral insufficiency*, the form of the left ventricle is somewhat different from that just described as occurring in aortic valvular and hypertensive disease. In mitral insufficiency, hypertrophy and dilatation are not initiated so predominantly in the outflow tract, but are generally most marked in the early stages in the beginning of the inflow tract under the mitral valve. I have had no opportunity to observe at the postmortem table whether dilatation and hypertrophy of the left ventricle is actually initiated *solely* in this part of the left ventricle just under the mitral valve. But the predominant dilatation and hypertrophy of the beginning of the inflow tract in mitral regurgitation is often evident in the roentgen picture as a prominence and rounding of the upper portion of the left border of the left ventricle, so that it appears to be enlarged upward and more nearly spherical than usual.

The Right Ventricle.—Under normal circumstances, the right ventricle forms the larger part of the anterior surface of the heart. However, it does not reach either of the lateral borders, being separated from the right border by the right auricle and from the left by a narrow strip of the left ventricle below and by the pulmonary artery and left auricular appendage above. Only exceptionally, in individuals with a low diaphragm, does the right ventricle form a small portion of the right border above the diaphragm. Because of this enclosed situation, there may be considerable hypertrophy of the right ventricle without any alteration in the size or shape of the heart as demonstrated by percussion or roentgen examination with dorso-ventral illumination.

In analogy with the course of events in the left ventricle, hypertrophy of the right ventricle starts in the terminal portion of the outflow tract, *i. e.*, the pulmonary conus (page 298). When of sufficient degree, this enlargement of the pulmonary conus fills out the concave recess in the left border of the heart between the left

ventricle and the aorta so that the middle segment of the left border becomes straight or even, if the enlargement of the conus is sufficiently pronounced, convex to the left Because it is seen most often in mitral disease, this change in the configuration of the left border of the heart is known as "mitralization." The best example of mitralization due entirely to the enlargement of the right ventricle proper is encountered in congenital pulmonary stenosis.



FIG 9 —Enlargement of the right ventricle manifested by straightening of the left border and broadening of the heart The barium-filled esophagus is bent to the right by the dilated left auricle Patient with mitral stenosis

However, in most of the conditions leading to hypertrophy of the right ventricle (mitral disease, antecedent left-sided failure, emphysema, and peculiarly enough some cases of pulmonary stenosis) there is accompanying dilatation of the pulmonary artery, and in the case of mitral disease of the left auricular appendage as well The result is that the filling out of the concavity of the left border ("mitralization") is generally due not only to the enlargement of the

pulmonary conus but also to dilatation of the pulmonary artery and left auricular appendage. Indeed, it seems that most often the dilatation of the pulmonary artery is the most important factor in producing a prominent convexity of the middle arc of the left border Lesser degrees of enlargement of the pulmonary conus are often more clearly visualized by rotating the patient slowly toward



Fig 10 —Marked enlargement of the pulmonary artery in mitral stenosis

the right anterior oblique position (right shoulder to the screen), but it should be remembered that even normally the pulmonary conus may be prominent in this position. On some occasions, in which marked hypertrophy of the right ventricle is unaccompanied by dilatation of the right auricle, the right ventricle may be visualized at the right border of the heart just above the diaphragm during

inspiration when the patient is rotated slightly toward the right anterior oblique position Marked hypertrophy of the right ventricle may be evidenced, even before it can be demonstrated roentgenologically, by epigastric pulsation, the latter must be differentiated from hepatic pulsation.

It seems doubtful that hypertrophy of the right ventricle is ever considerable enough to cause, *per se* and without dilatation, increase



FIG 11 —Bulging of the dilated left auricle into the retrocardiac space Patient with mitral stenosis, right shoulder to the screen

in the maximum transverse diameter sufficiently above the normal to be unequivocally pathological But when dilatation supervenes to any considerable extent, the heart is broadened The enlarging right ventricle displaces the right auricle to the right with resultant broadening of the heart in this direction The left portion of the dilating right ventricle reaches the left border of the heart, taking the place of the left ventricle in forming this border, and in extreme cases may even form the apex of the heart The result is an increase

in the transverse diameter of the heart which extends far beyond the normal limits to both the right and the left. Since marked dilatation of the right ventricle is practically always accompanied by dilatation of the right auricle, the consequence is that, unless the left ventricle is also markedly enlarged, the cardiac shadow extends as far or further to the right as to the left of the mid-line and presents a roughly triangular outline with an almost horizontal base on the diaphragm. Enlargement of the right ventricle increases the antero-posterior diameter of the heart, as can be seen by examination in the left anterior oblique and lateral positions. But it is



FIG 12 — The same patient as FIG 9 with the right shoulder to the screen. The enlarged left auricle obliterates the retrocardiac space and displaces the barium-filled esophagus backward

to be remembered that in mitral disease the principal cause of increase in the antero-posterior diameter is dilatation of the left auricle

Enlargement of the right ventricle results in rotation of the heart. This is due to the fact that the enlarging right ventricle meets with resistance from the chest wall in front and from the diaphragm below In consequence, as described by Assmann,[1] the heart is rotated around its long axis in what would be a clockwise direction when viewed from the apex. The results of the rotation of the heart have been carefully studied by Assmann, who described

them as follows: The first part of the aorta and the pulmonary artery are rotated to the left, the left auricular appendage and the left ventricle posteriorly, the left auricle to the right and anteriorly, and the right auricle anteriorly. This rotation plays a significant part in producing the straightening of the left border and the broadening of the heart to the right that characterizes "mitralization."

The Left Auricle.—In health, the left auricle lies almost entirely on the posterior aspect of the heart. The only portion of the chamber which reaches the lateral borders of the heart is the left auricular appendage, the tip of which curves anteriorly so as to form part of the left cardiac margin between the pulmonary artery above and the left ventricle below. And in all but the most extreme degrees of dilatation of the left auricle, the auricular appendage remains the only part of the chamber that can be visualized by means of sagittal illumination Assmann has found by comparative radiographic and postmortem studies that when the left auricle is dilated, the auricular appendage forms at most a thin margin to the left of the pulmonary conus, which is itself enlarged in practically all cases of left auricular dilatation and serves to hide all but the tip of the auricular appendage Indeed, in cases of mitral disease, the rotation of the heart due to enlargement of the right ventricle (page 370) may be sufficiently marked to displace the auricle so far posteriorly and to the right that even the dilated auricular appendage is masked on dorso-ventral illumination by the enlarged pulmonary conus When, in a patient with mitral disease, one is able to demonstrate by percussion a convex protrusion of the left cardiac border in the vicinity of the third interspace, it is the pulmonary conus that causes the dulness and not the left auricle.

The reason that the left border of the heart is so little affected by dilatation of the left auricle is that the enlargement of this chamber, which may attain prodigious extent (page 493), occurs behind the posterior aspect of the rest of the heart The expanding left auricle fills out the retrocardiac space between the heart and the vertebral column. Furthermore, the rotation of the heart due to the almost invariably concomitant enlargement of the right ventricle (page 370) occurs in such a direction as to rotate the dilated left auricle to the right and, in extreme dilatation, anteriorly The result is, as pointed out by Assmann, that the dilated left auricle penetrates between the right auricle anteriorly and the hilus of the right lung posteriorly, and in extreme cases reaches to the right of the right auricle so as to form part of the right border of the heart.

It is only in exceptional cases that this course of events can be made out by *fluoroscopy or a film taken with dorso-ventral illumina-*

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the examination be performed in the right posterior oblique position (patient's back to the screen, right shoulder to the screen), the patient being rotated at an angle of about 50 degrees. Assmann advises the use of the right anterior oblique position (patient facing screen, right shoulder to screen) with rotation of about 70 degrees. The latter position has seemed to me the more useful because of the greater normal width of the retrocardiac space. In these posi-

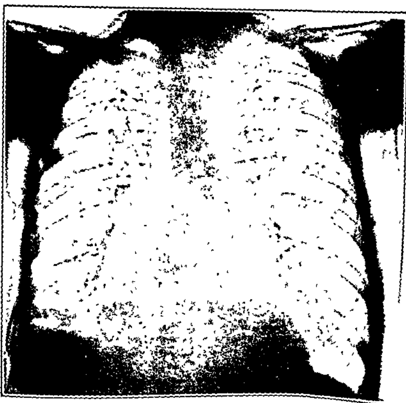


FIG 14.—Enlargement of the right side of the heart secondary to pulmonary fibrosis and emphysema in a patient with chronic cough, cyanosis and polycythemia. Note the prominence of the pulmonary arteries at both hiluses

tions the left auricle forms part of the posterior border of the cardiac shadow. Enlargement of the chamber is revealed by increasing convexity of the posterior border of the cardiac shadow which impinges on the retrocardiac space and with marked dilatation merges with the vertebral shadow, being bounded above and below by relatively clear areas. With extreme dilatation the left auricle may obscure the retrocardiac space down to the diaphragm.

even on deep inspiration. Unfortunately, the delineation of the left auricle on oblique illumination is often rendered difficult or impossible by accompanying engorgement of the pulmonary vessels which darken the lung fields and consequently the retrocardiac space, and dilatation of the right auricle or other parts which merge with the shadow of the dilated left auricle.

The expanding left auricle may impinge on certain of the neighboring structures and produce consequences which facilitate recognition of the dilatation:

1 The esophagus is compressed and displaced, most often posteriorly, sometimes also to the right or more rarely to the left. By giving the patient barium and watching its descent, most advantageously as a rule in the right anterior oblique position, the displacement of the esophagus is readily recognized when present.

2 As a result of marked dilatation of the left auricle, the two main bronchi are spread apart and assume a more horizontal course which can sometimes be visualized fluoroscopically. The trachea is also displaced dorsally.

3. On rare occasions, dilatation of the left auricle may produce sufficient compression of the left lung to result in a small area of dulness between the vertebral column and the spine of the left scapula

The Right Auricle.—The right auricle forms the right border of the heart, extending from the diaphragm to the shadow of the superior vena cava.* Enlargement of the right auricle is revealed by broadening of the heart to the right Indeed marked enlargement of the heart to the right is almost always attributable to the right auricle, for hypertrophy of the right ventricle causes at most a moderate extension of the cardiac silhouette to the right, while when the right ventricle is dilated the right auricle is also enlarged That extension of the cardiac shadow to the right may also be due to a large left auricle was mentioned above, and the differential criteria discussed.

RELATION OF THE CARDIAC PULSATIONS TO THE FUNCTIONAL CAPACITY OF THE HEART

A priori, it might be thought that the fluoroscopic study of the pulsations of the heart would afford a valuable index of the functional capacity of the organ Actually, however, this is true to only a limited extent because of the variety of factors that affect the amplitude and other characteristics of the cardiac pulsations in both health and disease (see Roesler[16]).

* The right border of the vascular pedicle has generally been thought to be formed by the superior vena cava However, Spillane's[11] observations indicate that the lower third of the right border of the vascular pedicle may be formed by the ascending aorta

Normally, the cardiac pulsations are best seen in that portion of the left border of the heart which is formed by the left ventricle. With each systole the border of the left ventricle moves in about 2 to 6 mm, to return more slowly in diastole A systolic expansion is generally plainly visible in the pulmonary artery and aorta The amplitude of movement of the right border of the heart, which is formed by the right auricle, is generally much smaller than that of the left, according to Dietlen and others, it generally consists in a minute presystolic movement inward due to auricular systole, followed by a systolic movement in the same direction resulting from traction on the right auricle by the contracting right ventricle But these movements of the right border are generally so small as to be difficult to follow and time by even an expert radiographer The same is true of the presystolic contraction of the left auricular appendage in the angle between the left ventricle and the pulmonary conus However, in heart block one can often see that there is more than one contraction of the right auricle to each contraction of the left ventricle. The superior vena cava usually shows practically no pulsation in the erect position in health, but when recumbent or in individuals with a short thorax and high diaphragm (Roesler[15]) a wavy pulsation may be evident in this vessel Sometimes, the contraction of the lower border of the right ventricle can be seen through the gastric bubble, it is of about the same amplitude as that of the left ventricle

The amplitude of pulsation of a chamber is largely governed by two factors, namely, the output per beat (stroke volume) and the size of the chamber.

1. *The stroke volume of the chamber* Quite obviously, other factors being the same, *the larger the output per beat the greater the amplitude of the pulsations.* This is the reason why in free aortic or mitral regurgitation the left ventricular pulsations are of great amplitude, for the left ventricle must eject into the aorta at each beat not only the "effective" stroke volume but also the volume of blood regurgitated during diastole. The result is that in free aortic or mitral regurgitation the amplitude of pulsation of the left border is greatly increased while that of the right border is unaffected The relation of the heart rate to the amplitude of pulsation is also important because of its effect on the stroke volume. Since with the same minute volume the stroke volume is inversely proportional *to the heart rate, it is evident that with tachycardia the amplitude of pulsation is decreased and with bradycardia increased* Indeed, in heart block the amplitude of pulsation of the left border may be as much as 15 or 20 mm. On the other hand, in paroxysmal tachycardia the cardiac silhouette may appear immobile.

2. *The size of the chamber* also has a profound effect on the amplitude of the pulsations For the larger the size of the chamber,

the smaller the distance that the wall must move to expel the same volume of blood (page 312). The result is that, in general, the amplitude of pulsation is inversely proportional to the size of the chamber Thus, the small "drop" heart of the asthenic individual has a more ample excursion than the massive heart of the sthenic athlete In heart failure, the affected chamber (or chambers) is increased in volume as a result of dilatation and the stroke output is diminished because of myocardial weakness and the resulting tachycardia As a result of summation of these factors, the amplitude of the cardiac pulsations is generally much diminished. Indeed, in rapid, greatly dilated hearts, the movements of the left border may be hardly discernible However, if the failure occurs in the presence of free aortic or mitral regurgitation, the increase in systolic discharge due to the leak may counteract these factors and the pulsations may be very prominent despite severe symptoms of cardiac insufficiency. In some other—rather unusual—cases in which an obviously failing hypertensive or arteriosclerotic heart presents pulsations of considerable amplitude, a similar action of relative mitral insufficiency, itself due to the failure, may be responsible. In isolated left ventricular failure, the pulsations of the left border may be much less than those of the right. The increase in the amplitude of pulsation of the left border when the insufficient heart is slowed by digitalis is often striking

Another characteristic of the cardiac pulsations, which is of interest although difficult to study except by kymography (page 381) is the rate of the movement When the heart has to pump against a heavy load—especially in aortic stenosis but also sometimes also to a less extent in hypertension—the systolic inward movement of the left border seems to be slower than usual. On the other hand, in Graves' disease and also in some patients with "neurocirculatory asthenia," the wall of the left ventricle seems to move with great rapidity which, with the accompanying tachycardia, imparts to the heart under the fluoroscope what might be described as an agitated appearance. However, the amplitude of the cardiac contractions in Graves' disease generally does not appear to be increased

In some cases of constriction of the heart due to mediastinopericarditis, the pulsations are hardly visible; this is especially significant if the heart is small.

THE DIMENSIONS OF THE HEART

In the early days of cardiac roentgenology, major emphasis was laid on the absolute dimensions of the heart. Great pains were taken to measure—in the orthodiagram and later in the teleoroentgenogram—various dimensions of the heart in large series of normal individuals of both sexes and of different ages, weights, and

heights. The aim was to ascertain the normal variations and thereby afford an adequate basis for the detection of minor degrees of cardiac enlargement. Three varieties of measurement have been studied:

1. *Linear dimensions*· The most frequently used of these have been the right and left median and the longitudinal diameters.

The right and left *median diameters* are, respectively, the perpendiculars dropped from the most lateral points of the right and left borders of the heart to the mid-line. The sum of the right and left median diameters is known as the *transverse diameter.* Since the right and left median diameters generally do not lie at the same level, they have to be measured separately and added to obtain the transverse diameter. As a rough approximation, the transverse diameter of the heart in health may be taken to be about one-half the maximum internal diameter of the chest, which is the horizontal line between the two most lateral points of the lung fields Actually, however, this ratio of the transverse diameter of the heart to that of the chest is greater in individuals with transversely placed heart than in those with more vertical organs Indeed one encounters seemingly healthy individuals with vertical hearts in whom the transverse diameter is only one-third that of the lung fields, and almost equally broad variations in the opposite direction occur in healthy persons with transverse hearts Of the components of the transverse diameter, the left median diameter is generally about twice the right median diameter Here again, however, the ratio is affected by the habitus of the patient, being greater with a transversely placed heart and less as the position of the organ approaches the vertical.

The *longitudinal diameter* of the heart is the distance from the apex to the point on the right border at the junction of the right auricle and the great vessels. The longitudinal diameter of the heart in health is generally a little longer than the transverse diameter; according to Dietlen,[4] the ratio averages 11 to 10 Generally speaking, distortion of the ratio in favor of the transverse diameter speaks for predominant enlargement of the right heart, while the reverse is true when the enlargement is due to the left ventricle.

A number of other linear dimensions of the cardiac silhouette as seen on dorso-ventral illumination (indices of the breadth of the base of the heart, chords of the arcs of the cardiac borders, etc.) have also been studied. Further, the antero-posterior diameter of the heart as observed in the lateral view of the heart and the diameter of the aorta have been investigated. As yet, however, none of these measurements seem of notable clinical value; details regarding them may be obtained in the publications of Vaquez and Bordet[20]

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heights The aim was to ascertain the normal variations and thereby afford an adequate basis for the detection of minor degrees of cardiac enlargement. Three varieties of measurement have been studied:

1. *Linear dimensions* The most frequently used of these have been the right and left median and the longitudinal diameters.

The right and left *median diameters* are, respectively, the perpendiculars dropped from the most lateral points of the right and left borders of the heart to the mid-line The sum of the right and left median diameters is known as the *transverse diameter.* Since the right and left median diameters generally do not lie at the same level, they have to be measured separately and added to obtain the transverse diameter. As a rough approximation, the transverse diameter of the heart in health may be taken to be about one-half the maximum internal diameter of the chest, which is the horizontal line between the two most lateral points of the lung fields. Actually, however, this ratio of the transverse diameter of the heart to that of the chest is greater in individuals with transversely placed heart than in those with more vertical organs Indeed one encounters seemingly healthy individuals with vertical hearts in whom the transverse diameter is only one-third that of the lung fields, and almost equally broad variations in the opposite direction occur in healthy persons with transverse hearts Of the components of the transverse diameter, the left median diameter is generally about twice the right median diameter. Here again, however, the ratio is affected by the habitus of the patient, being greater with a transversely placed heart and less as the position of the organ approaches the vertical.

The *longitudinal diameter* of the heart is the distance from the apex to the point on the right border at the junction of the right auricle and the great vessels The longitudinal diameter of the heart in health is generally a little longer than the transverse diameter; according to Dietlen,[4] the ratio averages 11 to 10 Generally speaking, distortion of the ratio in favor of the transverse diameter speaks for predominant enlargement of the right heart, while the reverse is true when the enlargement is due to the left ventricle.

A number of other linear dimensions of the cardiac silhouette as seen on dorso-ventral illumination (indices of the breadth of the base of the heart, chords of the arcs of the cardiac borders, etc.) have also been studied Further, the antero-posterior diameter of the heart as observed in the lateral view of the heart and the diameter of the aorta have been investigated. As yet, however, none or these measurements seem of notable clinical value; details regarding them may be obtained in the publications of Vaquez and Bordet[20]

and Roesler.[16] Extensive tables of the various linear measurements are given by White,[21] Hodges and Eyster[7] and Kurtz.[9]

2. The *surface area* of the cardiac silhouette on dorso-ventral illumination may be estimated by transferring the outline to squared paper and counting squares or by means of a planimeter. However, an inaccuracy is introduced by the fact that the upper and lower borders of the cardiac shadow can only be approximated, there being no complete differentiation from the vascular shadow above and that of the liver below. Detailed tables of the surface area of the heart in relation to other bodily measurements are given by Bardeen[2] and by Kissane.[8] It was hoped that the cardiac area would form a more delicate index of abnormality in the size of the heart than do the linear measurements. But this hope has hardly been fulfilled.

3. The *volume* of the heart was estimated by Rohrer[17] by means of a formula based on the surface area and the antero-posterior diameter as observed in the lateral view of the heart. Since the heart has an irregular outline and is not of geometric configuration, it is obvious that such a formula can give only approximate results, although Rohrer estimates the error at less than 15 per cent. Recently, Liljestrand[10] and his associates have found the normal heart volume to vary between 7 and 13 cc. per kilogram body weight. With so wide a normal variation, it does not appear that the measurement of the volume of the heart can help in the detection of the lesser degrees of cardiac enlargement.

Factors Influencing the Dimensions of the Heart in Health.—Among the most important causes of the variability of the cardiac measurements in health are the following:

1. **The Constitutional Habitus of the Individual.**—The shape of the thorax is a characteristic which notably affects the position and measurements of the heart. Individuals with broad short chests generally have transversely placed hearts with relatively large transverse diameters. On the other hand, those of the asthenic habitus with long, thin chests usually have vertically disposed hearts with short transverse diameters ("drop heart"). In an individual of the latter constitutional type, very considerable enlargement of the heart is needed to cause the transverse diameter of the heart to reach even the upper limit of normal.

2. **The Position of the Diaphragm.**—Elevation of the diaphragm causes the heart to assume a more transverse position with consequent increase in the transverse diameter and a larger proportion of the total silhouette to the left of the mid-line; depression of the diaphragm has the reverse effect. These effects of the position of the diaphragm on the cardiac silhouette are well seen during the respiratory movements. Similarly, the transverse diameter is greater and the longitudinal shorter in the reclining posture than when erect. The position of the diaphragm is probably an impor-

tant element in the causation of the constitutional variations in the form of the heart mentioned in the preceding paragraph A high diaphragm due to increase in intra-abdominal fat as part of general obesity may cause a transverse position of the heart with increased transverse measurements; in such cases, an unjustified diagnosis of cardiac enlargement is often made Meteorism may similarly cause a transverse position of the heart. On the other hand, the low diaphragm of many patients with bronchial asthma and pulmonary emphysema causes the heart to assume a vertical position with small transverse diameters. It is for this reason that the heart of the asthmatic generally appears small to the roentgenologist, though at postmortem hypertrophy of the right ventricle is often present Moreover, in these patients the cardiothoracic ratio is also distorted by the increased volume of the lungs.

3 **The Muscular Development of the Individual** —It was seen above that the weight of the heart tends to vary *pari passu* with the mass of the skeletal muscles (page 307) The result is that hard-working and athletic individuals generally have larger hearts than those of sedentary habits. The difference in muscular development probably explains the fact that the cardiac measurements in the male average larger than in the female

4 **Weight** —In large statistical series, there is a fairly close, direct correlation between body weight and the size of the heart It seems, however, this is because heavier individuals tend to have a greater muscle mass Where the increase in weight is due purely to adiposity, the heart is not correspondingly increased in size and may indeed be small However, even in such obese individuals enlargement of the heart may be simulated because of a transverse position of the organ resulting from a high diaphragm

5 **Height** —Statistically, there is also a direct, though not very close, correlation between stature and the size of the heart But this is also, apparently, merely a consequence of greater muscle mass. One sees many tall persons of asthenic habitus in whom the heart appears small because of its vertical position and may indeed be a typical "drop heart."

6 **Age.**—The silhouette of the heart in health varies with age In early childhood, the heart is actually larger in relation to the body weight and, further, the higher position of the diaphragm tends to place it in a more transverse position With the rapid growth in height during adolescence, the heart often assumes a vertical position with relatively small transverse diameter Toward the end of middle life and after this, the heart assumes a more transverse position with increase in the transverse diameter. Moreover, the heart is situated more in the lowest part of the thorax than normally, often conveying the impression of lying on the diaphragm. This transverse, low position of the heart in most elderly persons seems

to be at least largely the result of elongation of the arteriosclerotic aorta, which plays a part in maintaining the position of the heart. Further, the diaphragm is situated higher with advancing years, which also helps the heart toward a transverse position. In the senium, the heart participates in the general atrophy of the organs.

7. **Nutritional State**.—Experimentally, it has been found that the heart atropies as a result of severe and protracted undernutrition. Similarly, in persons who have succumbed to carcinomatous cachexia the heart is often found to be atrophied at necropsy. This may not be discernible on roentgen examination during life because of other factors, notably anemia, which lead to dilatation of the heart (page 577)

8. **Transitory Influences.**—There are many factors which lead to transitory changes in the size of the heart. Among these may be mentioned various respiratory gymnastics, changes in circulating blood volume, and variations in pulse rate.

During the Valsalva experiment (forced expiration with the glottis closed), the heart is seen under the fluoroscope to become smaller in consequence of the diminished venous return resulting from the increased intrathoracic pressure. On the other hand, in the Mueller experiment (forced inspiration with a closed glottis), the heart increases in size.

Experimentally, it has been shown that sudden increase in circulating blood volume by intravenous infusion is followed by enlargement of the heart which persists as long as the added fluid remains within the circulation. And the diminution in circulating blood volume that results from copious venesection has been observed to be accompanied by a diminution in the size of the heart. It seems probable that this influence of the circulating blood volume on the size of the heart is largely mediated through the venous return, a higher venous pressure resulting in dilatation and *vice versa*. For there are cases of polycythemia vera with very high circulating blood volume in which the heart is not enlarged; in such cases I have observed the venous pressure to be normal

Acceleration in pulse rate tends to diminish the size of the heart, the diminution in size being presumably an accommodation to the smaller stroke volume The decrease in size of the heart accompanying marked tachycardia was shown by Moritz,[13] who made orthodiagrams of the heart before and after the administration of a large dose of atropine Meek[12] found in dogs that the diastolic size of the heart decreases as the rate becomes more rapid. In the first stages of severe attacks of paroxysmal tachycardia, the heart can often be observed to be small, though if the paroxysm lasts long enough dilatation supervenes as a result of weakness of the myocardium.

Clinical Limitations of Cardiac Measurements.—As a result of the operation of the factors enumerated in the preceding section, *the zone of the cardiac measurements in health is so broad that incipient pathological enlargement of any of the dimensions does not fall without the normal range.* Consequently, the utility of cardiac measurements to the clinician is very limited, indeed, I do not recall any instance in which the numerical measurements of the heart added in any substantial fashion to the information obtained by fluoroscopy and the inspection of the teleoroentgenogram When the enlargement is so great as to be revealed unequivocally by the absolute value of the measurements, it is immediately obvious on fluoroscopy or examination of the film The clinician is best served by the study of the form and size of each of the chambers individually, using the criteria described above (pages 362 to 374), and little is added by the measurements. Such "chamber by chamber" investigation of the heart affords an insight into the nature of the disturbances in circulatory dynamics that can be obtained in no other way.

There seems to be little need for orthodiagraphy, the mastery of which demands considerable practice (see Kurtz[9] for technic and results). Fluoroscopy, with the addition, if needed, of the teleoroentgenogram, would seem to serve practically all clinical purposes Actually, orthodiagraphy is being used less and less in this country.

Roentgen Kymography.—This method records the movements of the borders of the roentgen shadow of the heart A metal sheet with closely spaced, horizontal slits is interposed between the chest and a moving film During the exposure of one second the film moves vertically a distance a little less than that between two slits The result is that the component of the movement of the cardiac borders parallel to the longitudinal direction of the slits is recorded in the form of wave-like excursions of the cardiac silhouette *By the study of the waves thus produced along the borders of the cardiac shadow, much information can be obtained regarding the time in the cardiac cycle, amplitude, and rate of movement of the individual chambers of the heart, aorta, and pulmonary artery* The method promises greatly to enhance our knowledge of the dynamics of the heart beat in health and disease Among the conditions in which kymography is sometimes of diagnostic value are aneurysm of the aorta, pericardial effusion, constrictive pericarditis, myocardial infarction, aneurysm of the ventricle, and the myxedema heart For details, the reader is referred to Hirsch and Gubner,[6] Bordet and Fischgold,[1] and especially Gubner, Crawford *et al*[5]

Visualization of the Individual Cardiac Chambers—Recently, Robb and Steinberg[14] have achieved a notable advance by developing a method for the visualization of the individual chambers of the heart, the pulmonary circuit, and the great vessels They inject 20 to 45 cc of a 70 per cent solution of diodrast into an antecubital vein, films taken three to five seconds after show filling of the right auricle, the right ventricle, and the pulmonary arterial tree The left side of the heart and aorta are visualized from six to sixteen seconds after injection, the time in the individual case is indicated by the cyanide circulation time (page 51) For the numerous interesting details revealed by this method, which is as yet only in its infancy, the reader is referred to Robb and Steinberg

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CHAPTER XXI

GALLOP RHYTHM

GALLOP RHYTHM* is an unequivocal auscultatory sign of a failing heart. Though by no means invariably perceptible in even extreme *cardiac failure, and sometimes closely simulated by other sounds,* nevertheless the appearance of gallop rhythm is often the first objective evidence that the heart is embarrassed Despite this fact and the voluminous literature on the subject. it has not seemed to me that appreciation of the significance of gallop rhythm is sufficiently widespread in the profession. It has been my experience that internes are not nearly as keen in detecting gallop rhythm as they are in eliciting murmurs. This is the more unfortunate because gallop rhythm is so often an early sign of cardiac insufficiency in arteriosclerotic and hypertensive heart disease, probably the most common basis of heart failure in at least most parts of the United States. And we shall seen that gallop rhythm expresses the very nature of heart failure.

Historical.—What is now termed gallop rhythm seems to have been first observed by Charcellay,[5] a physician of Tours, in 1838. In a patient with chronic renal disease and a failing heart, he heard a third sound during diastole, and realized that this supernumerary tone coincided with the contraction of the auricles. According to Potain,[25] the term *bruit de gallop* was first used in 1847 by Bouillaud. The designation gallop rhythm, now in general use, was applied by Traube [35] General appreciation of the sign dates from the classic descriptions of Potain[26] and the studies of his pupils Extensive reviews have been published recently by Holt[14] and Laubry and Pezzi,[19] and a splendid phonocardiographic analysis by Wolferth and Margolies.[38]

CLINICAL CHARACTERISTICS OF GALLOP RHYTHM

Gallop rhythm is characterized by the occurrence of three heart *sounds during each cardiac cycle. The supernumerary sound is* actually independent and not merely a splitting or reduplication of either of the two sounds usually heard. The resulting cadence varies with the position of the added sound in the cardiac cycle, with the rate of the heart, and with the relative intensity of the three sounds. Very often especially with well-marked acceleration of the heart rate, it fully justifies the analogy with the gallop of a

* In the following the unmodified term gallop rhythm is used to connote diastolic gallop rhythm. Systolic gallop rhythm is far less common and apparently of no considerable clinical significance (page 395).

horse; in other cases, the rhythm has been described by the appellation canter or trot rhythm. There are, however, also instances in which the added sound, though separate and distinct, does not result in simulation of these equine cadences; this is especially apt to be the case when the rate of the heart is not accelerated. Nevertheless, the pathogenesis of the added sound appears to be the same as when the rhythm is that of a gallop—the rhythm impressed on the ear may vary from day to day simply as a function of the rate—so that it seems wise to include such rhythms under the most widely used appellation of gallop rhythm. The extra sound of gallop rhythm occurs almost always in ventricular diastole, after the second and before the first sound of the heart. Systolic gallop rhythm, in which the added tone follows the first sound, is rare and will be discussed separately (page 395). The sound may occupy any position in diastole: presystolic, mesodiastolic and protodiastolic gallop rhythms. The significance of the location in diastole will be discussed in conjunction with the pathogenesis, where it will be pointed out that it may be markedly affected by the rate of the heart and the auriculo-ventricular conduction time. Potain originally described presystolic gallop rhythm as much the most common variety, most subsequent writers agree with this and it has also been my impression, although I have kept no statistics. On the other hand, White[38] found that in a series of cases there were 64 instances of protodiastolic gallop rhythm as contrasted with but 12 pre-systolic and 4 systolic gallops. These differences of opinion are probably largely due to difficulties in timing the location of the extra sound in diastole when the heart is rapid. With the phonocardiograph, which enables accurate timing, Wolferth and Margolies found that at one time or another 37 of their patients had presystolic and 29 protodiastolic gallop.

On very rare occasions, both presystolic and protodiastolic sounds are present, so that four heart sounds are heard. Of course, the differentiation and timing of four sounds in a cycle is difficult, and it may be that sound tracings will reveal that this combination of presystolic and protodiastolic gallop rhythms is not a great rarity; such tracings have been published by Wolferth and Margolies.

In presystolic gallop rhythm the accent is usually such as to result in an anapest, in protodiastolic of a dactyl. However, these accentuations are far from constant.

The gallop sound was originally described by Potain as a dull one, like a thud, in fact, the older observers, who applied the ear to the chest or used a wooden stethoscope, noted that it makes more of a tactile than an auditory impression on the ear. The pitch is low and, correspondingly, sound tracings show that the vibration frequency is relatively small. Potain and other French clinicians have stated that the gallop sound is not transmitted

through a flexible stethoscope, but I generally have little difficulty in perceiving it with the ordinary Bowles model. It is true that there are cases in which the sound is better heard with the naked ear, probably largely because of the added tactile impression.

The intensity of the gallop sound varies. Most often, it is rather faint and may just surpass the threshold of audibility However, there are also cases in which it is loud Connor[5] describes 10 cases in which the added sound of protodiastolic gallop rhythm was much the loudest of the three sounds of the cardiac cycle Since reading his description, I have made a number of similar observations. The loudness of the extra sound may vary with the phases of respiration.

The gallop sound is generally loudest close to the apex In some cases, the area of audibility of the gallop rhythm is sharply localized at the apex or a circumscribed area a little mesial to it But a loud gallop may be audible all over the precordium though it is rarely transmitted much beyond it. In some cases, though not all, gallop rhythm is heard very clearly over the right jugular bulb But it is to be remembered that not rarely a triple sound is normally audible in this region as a result of good transmission of the auricular sound. When gallop rhythm accompanies pericardial friction, there may be a triple division of the rub, the triple pericardial friction observed by Salter [28]

Johnson[16] long ago noted that the site of gallop rhythm may be conditioned by the nature of the underlying process He observed that "in cases of emphysema with impeded pulmonary circulation, the reduplication is more distinctly heard at the right margin and the lower end of the sternum than to the left" Since then, following Potain, French clinicians have differentiated right- and left-sided gallops. According to this view, a gallop originating in the left side of heart is best heard in the area described in the preceding paragraph, while one due to failure of the right heart (as in emphysema heart) is best heard in the xiphoid region I have heard only a few instances of clear-cut right-sided gallop. It should be borne in mind, in this connection, that quite often gallop is best heard close to the sternum in left heart failure, though generally not as low as in typical right-sided insufficiency. Wolferth and Margolies described two cases with both right- and left-sided gallop

Often, the gallop sound is accompanied by a palpable and sometimes also visible *impulse* This impulse may be very prominent and give the impression to the palpating hand of a double apex beat. It was mentioned above that the impulse may be more prominent than the sound In eliciting gallop rhythm, one should always employ simultaneous auscultation and palpation. This may be best accomplished by auscultating with the naked ear. I have

often derived considerable help from the impulse communicated to the fingers which hold the Bowles stethoscope lightly in place.

Gallop rhythm is most characteristically appreciated in the presence of moderate or marked tachycardia. While the extra sound sometimes occurs in a heart that is not accelerated, the impression on the ear is rarely that of gallop. At heart rates of 130 or over, diastole is so short that it is difficult or impossible to separate the extra sound with certainty. The effect of the onset of auricular fibrillation on gallop rhythm will be discussed below.

Exercise often serves to bring out gallop rhythm. Sitting the patient up and down a few times often helps in eliciting the sign in the first beats after the exercise. It is often heard better with the patient lying on the left side

PATHOGENESIS OF GALLOP RHYTHM

The mechanism of gallop rhythm has offered a fruitful field for speculation. A number of hypotheses regarding the origin of the extra sound—asynchronous contraction of the two ventricles (Sibson[29]), contraction of the left ventricle in two steps because of increased resistance in hypertension (D'Espine[8]), dissociation of the muscular and valvular components of the first sound (Bard[1]), etc —have been advanced, only to be abandoned as untenable. Details of the evidence against these and other hypotheses will be found in the reviews of Holt and Laubry and Pezzi.

As a result of many investigations, which have been analyzed and extended by Laubry and Pezzi, it has become clear that in addition to the rare instances of systolic gallop, *there are two pathogenetically distinct varieties of gallop rhythm:*

1. Gallop rhythm in which the extra sound coincides with auricular systole. According to Wolferth and Margolies, the extra sound in this variety of gallop rhythm occurs between 0.08 and 0.14 second after the beginning of the *P* wave of the electrocardiogram. This type is generally designated presystolic gallop, but it is not always presystolic in time and we shall term it *auricular gallop rhythm.*

2 Gallop rhythm in which the added sound is independent of auricular systole and corresponds to an accentuation of the normal third heart sound Wolferth and Margolies found that the supernumerary sound occurs beween 0.1 and 0 21 second, usually 0.13 to 0 18 second, after the beginning of the second heart sound This variety is usually designated as protodiastolic gallop rhythm but it may also occur later in ventricular diastole It will be termed *gallop rhythm due to a third heart sound.*

A third variety of gallop rhythm has been described by Wolferth and Margolies. They attribute the extra sound to the merging, as a result of tachycardia or prolonged auriculo-ventricular conduction

time, of the two preceding types of gallop, so that a single extra sound results. Wolferth and Margolies term this variety *summation gallop.*

Auricular Gallop Rhythm.—Charcellay, the first to describe gallop rhythm, noted that the adventitious sound appeared at the time of auricular systole. Later, the auricular origin of gallop rhythm was advocated in a brilliant paper by Johnson,[16] who held that "the contraction of a dilated, and especially of an hypertrophied auricle becomes sonorous, and that the first division of the double first sound in the cases under consideration is the result of the auricular systole."

Since then, it has been shown conclusively by a number of investigators that the added sound coincides with the systole of the auricle. Kriege and Schmall[18] long ago registered the venous pulse on a rotating drum while auscultating the heart and made a mark when the gallop tone was heard, the mark coincided with the auricular wave. Subsequently, Robinson,[27] Mueller,[24] Mond and Oppenheimer,[23] Laubry and Pezzi and others have noted that in the type of gallop rhythm in question, the cardiogram from the cervical and femoral veins and the hepatic tracing all exhibit a remarkably large excursion of the auricular wave Moreover, Lewis[20] and Mond and Oppenheimer have shown by means of simultaneous electrocardiograms and phonocardiograms that, allowing for the difference in time between the electrical and the mechanical phenomena, the extra sound in this variety of gallop rhythm coincides with auricular activity The investigations of Mond and Oppenheimer are of especial significance in this regard They found that "this extra (gallop) sound on the phonocardiogram always occurs at the same time as the latter half of the *P* wave of the electrocardiogram, and simultaneously with a large distinct wave of the apex beat and the *a* wave of the venous pulse" They were further able to show that in instances of gallop rhythm with partial auriculoventricular block, the adventitious sound still coincides with auricular systole. Another evidence of the rôle of auricular systole in the production of this form of gallop rhythm is the observation, repeatedly made, that the extra sound disappears with the onset of auricular fibrillation (what is not true of the other form of gallop rhythm).

There is thus evidence that.

1. The extra sound coincides with auricular systole
2. The extra sound results from auricular systole, else it would not disappear during auricular fibrillation.
3. There is an abnormally powerful contraction of the auricle, revealed by the large auricular excursion in the cardiogram, the cervical and femoral venous pulses, and the hepatic tracing.

The next question that arises is how the more forceful auricular

systole produces the supernumerary sound. That auricular systole can actually produce a sound is proved by the auricular tones that are often audible in many instances of complete heart block; in a recent case, the extra sound was as loud as the two normal sounds. Moreover, Bridgeman[2] showed that even in health the phonocardiogram reveals the presence of sound vibrations at the time of auricular systole, though these are generally too faint to be heard by the ear. Taquini and Braun[31] found that the auricular sound is always disclosed by esophageal auscultation. Now, whether the auricular sound is a muscle sound and emanates directly from the contracting auricular musculature, whether it is due to the distention by the auricular blood wave and consequent vibration of the ventricular wall, or both,* it would seem evident that a more powerful auricular systole must result in a louder auricular sound. That there is actually a more forceful auricular systole in patients with auricular gallop is indicated, in addition to the evidence mentioned above, by the very nature of the disturbance in circulatory dynamics. For the failure of the ventricle results in increase in the residual blood in the ventricle at the end of systole with a consequent increment in diastolic intraventricular pressure, so that the auricle has to contract more powerfully to drive blood into the ventricle.

It would thus seem that auricular gallop rhythm is an exaggeration of the sound normally produced by auricular systole due to more forceful contraction of the auricle Likewise, the distention of the ventricle by the strong auricular systole is probably the cause of the shock which is generally so prominent in gallop rhythm.

Another factor of importance in the pathogenesis of auricular gallop rhythm has been brought out by the investigations of Mond and Oppenheimer. They consider that since, in health, the muscle mass of the ventricle is soft as a result of diastolic relaxation at the time of auricular systole, it serves to dampen the auricular sound. They point to the small amplitude of the auricular wave in the sound tracing as indicative of this damping action of the ventricular myocardium. On the other hand, in cardiac failure the diastolic tension of the ventricle is increased (page 301) so that the damping action is less

* Phonocardiographic studies by Cossio and Fongi[6] show that the normal auricular sound often consists of two groups of vibrations, the first of which they attribute directly to auricular systole, the second to the tension of the ventricular wall by the auricular blood column Cossio and Fongi find that the normal auricular sound occurs so close to the sound produced by ventricular systole that the ear usually includes it with the latter in the first sound But the auricular sound may also be audible in the healthy subject as an independent sound, according to Cossio and Fongi this is the cause of most of the reduplications of the first sound heard in healthy subjects However, the observations of Wolferth and Margolies[40] show quite definitely that the usual mechanism of reduplication of the first sound is asynchronous contraction of the two ventricles

Lewis and Dock[21] interpret their observations as indicating that the gallop sound is due to tension of valve leaflets without an appreciable muscular element, but in his discussion of their paper Wolferth[41] cited strong evidence against this interpretation.

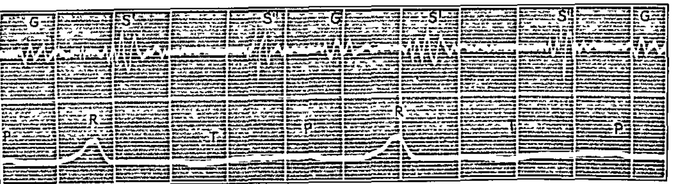


Fig. 15 —Simultaneous phonocardiogram and electrocardiogram in a patient with auricular gallop rhythm. The supernumerary sound (*G*) *follows* the *P* wave

Fig. 16 —Simultaneous phonocardiogram and electrocardiogram in a patient with gallop rhythm due to an accentuated third heart sound The extra sound (*G*) *precedes* the *P* wave

Finally, the prolonged auriculo-ventricular conduction time present in some, though not all, instances of gallop rhythm may participate in the audibility of the auricular sound. For the longer the interval by which the auricular tone is separated from the first sound, the more readily it will be heard as a separate sound.

Auricular gallop rhythm, it may be remarked parenthetically, is not always presystolic in time but may be mesodiastolic or even protodiastolic. This displacement of the extra sound may result from tachycardia or, less often, from partial heart block. For acceleration of the heart occurs principally through abbreviation of diastole The result is, since the interval between the auricular sound and the first sound is unaltered, that the extra sound occurs correspondingly earlier in diastole. Obviously, prolonged auriculo-ventricular conduction time in partial heart block will have the same effect.

The question of the relation of the Flint murmur in aortic insufficiency to gallop rhythm is discussed on page 478.

Gallop Rhythm Due to an Accentuated Third Heart Sound.—In this variety of gallop rhythm, the extra sound is usually protodiastolic in time However, when diastasis is shortened in tachycardia, the extra sound may be in the middle of diastole, much as we have just seen that the usually presystolic auricular gallop is displaced to middle or early diastole by tachycardia *

In discussing the origin of this type of gallop rhythm, a negative characteristic may first be pointed out *It is not produced by auricular contraction.* Lewis has published exquisite simultaneous electrocardiograms and phonocardiograms showing that the extra sound occurs prior to and independent of auricular activity. Laubry and Pezzi found in cardiograms that this type of gallop rhythm is not accompanied by a large auricular wave (as is the auricular variety) but that there is a large protodiastolic wave. Finally, this variety of gallop rhythm does not disappear during auricular fibrillation, an observation made by a number of investigators and recorded in a phonocardiogram by Lewis. I have heard the extra sound become much louder with the onset of complete arrhythmia

The cause of the gallop sound must therefore be sought in other than auricular contraction. The time relations of the adventitious sound indicate that it is an accentuation of the physiological third heart sound

* In other words, the extra sound in this variety of gallop rhythm is "linked" to the preceding second sound, while in auricular gallop rhythm the adventitious sound is linked to the following first sound. This is well seen when gallop rhythm due to an accentuated third heart sound occurs with auricular fibrillation Then it can readily be observed that the interval between the second sound and the gallop tone remains constant, while the time between the latter and the first sound varies

The *third heart sound* was demonstrated phonocardiographically by Einthoven[9] and first heard in normal subjects by Gibson[12] and Thayer.[23] Most of our knowledge of it is due to the last-named clinician He detected the sound in a majority of youthful individuals, but I have not been able to hear it nearly so often, the discrepancy is perhaps due to differences in auditory acuity or skill in auscultation. Thayer found that the third heart sound is best heard at the apex with the subject lying on the left side after slight exercise. The third heart sound occurs early in diastole, according to Bridgeman[7] about 0.16 second after the onset of the second sound It is accompanied by an elevation in the cardiogram (Robinson[17]) and sometimes by a palpable shock Hirschfelder[13] showed that it is also accompanied by a minute wave (*h* wave) in the venous pulse tracing, which has been confirmed by Bridgeman and others

The mechanism of production of the third heart sound is still unsettled. It occurs at the end of the period of rapid ventricular filling which marks early diastole. Hirschfelder attributes the third sound to elastic recoil of the ventricle at this time resulting in slapping together of the auriculo-ventricular valve flaps with resultant sound production

The interpretation of this form of gallop as an accentuation of the third heart sound is borne out by the cardiograms of Robinson and Laubry and Pezzi, which show that there is a marked enlargement of the protodiastolic wave which accompanies the third heart sound. Further, the *time of the gallop sound in early diastole*, so beautifully shown in the simultaneous electrocardiograms and phonocardiograms of Lewis, is such as to indicate strongly that it is an exaggeration of the physiological third heart sound

It was mentioned above that the physiological third heart sound occurs at the end of the protodiastolic period of rapid ventricular filling, and seems to be in some way produced by this filling. The exaggerated protodiastolic wave in the cardiograms of those with *this form of gallop rhythm* would indicate that the accentuation of the third heart sound is due to an increase in the pressure at which early diastolic filling occurs Since the pressure that produces the early diastolic filling of the ventricle is the venous pressure, protodiastolic gallop rhythm is thus indicative of increased venous pressure, *i. e.*, pulmonary venous pressure in the usual left-sided gallop. Hirschfelder cites experimental evidence indicating that the higher the venous pressure filling the ventricles, the more vigorously the auriculo-ventricular valves shut at the cessation of the flow. And it would seem reasonable that the more vigorous the tension of the valves, the louder the sound that will be produced.

DYNAMIC SIGNIFICANCE OF GALLOP RHYTHM

From the foregoing, it would seem clear that *gallop rhythm is an acoustic expression of the altered circulatory dynamics resulting from failure of one or both ventricles, much more often the left ventricle* As a result of ventricular failure, the residual blood in the ventricle at the end of systole is increased, with consequent elevation of

venous and intra-auricular pressure. If the left ventricle is insufficient, this occurs in the left auricle and pulmonary veins; if the right ventricle is at fault, the increase in pressure affects the right auricle and venæ cavæ. The result is that the diastolic filling of the ventricle in question takes place more forcefully, *i. e.*, under higher pressure. In some instances this is accomplished principally by means of a more powerful auricular systole, which results in the auricular type of gallop rhythm. Under other conditions, the increase in the force of early diastolic filling is predominant, so that the form of gallop rhythm due to accentuation of the third heart sound appears But the more intimate nature of the alterations in circulatory dynamics leading to the one or the other type of gallop rhythm remains to be elucidated.

OCCURRENCE OF GALLOP RHYTHM

Gallop rhythm was originally described by Potain as occurring in chronic nephritis And indeed classical gallop rhythm is most often and for the longest period observed in the failing heart of hypertension or coronary sclerosis But it was soon after pointed out by Fraentzel[19] that gallop rhythm also occurs when the heart fails in typhoid fever and other infections Actually, gallop rhythm may develop in failure of either the right or the left heart no matter what the underlying basis. Thus, it is seen in the cardiac insufficiency of hypertension, coronary artery disease, myocarditis, valvular defects, pericardial affections, kyphoscoliosis, emphysema and other chronic pulmonary and pleural diseases. Gallop rhythm may promptly document the onset of the acute cardiac failure of coronary thrombosis or acute glomerulonephritis, or it may develop after months or years of chronic myocardial insufficiency. It may be a transitory phenomenon during paroxysms of cardiac asthma.

Despite this ubiquitous appearance of gallop rhythm, it is to be emphasized that there are many cases of protracted cardiac failure in which gallop rhythm is never heard; this applies even to its favorite terrain, the hypertensive heart Of course, in valvular disease, notably mitral lesions, gallop rhythm is most often obscured completely by murmurs occupying diastole.

With improvement of myocardial insufficiency, gallop rhythm commonly disappears, this often occurs rapidly and strikingly in coronary thrombosis or under the influence of rest or digitalis in various forms of heart failure.

DIFFERENTIAL DIAGNOSIS OF GALLOP RHYTHM

The most common source of confusion is reduplication of the first sound. When the interval between the extra sound and the first sound is sufficiently long, the question is settled in favor of the

abnormal character of the sound. Wolferth and Margolies state that the interval between the two elements of a reduplicated first sound does not tend to exceed 0.07 second, while in most instances of gallop rhythm the interval is between 0 08 and 0 14 second. Of course, clinically one must depend on the ear, which is facilitated by the fact that when the interval between the extra sound and the first sound is relatively long in comparison to the totality of diastole the cadence tends to assume that of a galloping horse But there is a borderland in which it is difficult or impossible to state from auscultation alone whether the extra sound has pathological significance, and one must judge by the accompanying phenomena Moreover, even when the interval between the adventitious sound and the first sound is short, and the cadence is not that of a gallop, it is not necessarily true that the extra sound is physiological and of no clinical significance One not uncommonly observes that splitting or "impurity" (by which is usually meant prolongation with a tendency to splitting) of the first sound appears with heart failure and disappears as the state of the heart improves. I have repeatedly noted, in following the course of what was originally a typical gallop rhythm, that as the adventitious sound became fainter and was on its way to disappearing, it made the impression on the ear of being very close to the first sound, and if heard for the first time would be classed as a split sound. In such cases, a phonocardiogram shows that the extra sound is presystolic in time and auricular in origin, and not the first of the two elements of a split first sound, both of which are systolic in time It should be remembered (King and McEachern[17]) that bundle-branch block sometimes, though by no means always, results in an often wide splitting of the first sound, which is an indication of asynchronous contraction of the ventricles, does not imply heart failure, and should not be confused with gallop rhythm. The split first sound of bundle-branch block may be accompanied by a "double apex beat" (King and McEachern) and thus simulate the shock of gallop rhythm Potain[25] pointed out that physiological reduplication of the first sound becomes more marked toward the end of expiration and may disappear during inspiration. However, I have rarely found respiratory variability of any considerable aid in differentiating gallop rhythm from a reduplicated first sound.

Especially in middle-aged individuals with hypertension, the differentiation of presystolic gallop rhythm from the presystolic murmur of mitral stenosis may be a matter of some difficulty. It should be remembered, in this connection, that left ventricular failure in hypertension can lead to well-marked "mitralization" of the cardiac silhouette on dorso-ventral illumination. The presystolic Flint murmur in aortic regurgitation may also simulate gallop rhythm (page 478).

Reduplication of the second sound at the base of the heart either physiologically, in bundle-branch block, or in systemic or pulmonic hypertension is scarcely likely to be confused with protodiastolic gallop rhythm

The opening click of the mitral valve in mitral stenosis (page 516) may closely simulate gallop rhythm, but can usually be differentiated by the accompanying signs.

In adhesive mediastino-pericarditis, supernumerary sounds simulating gallop rhythm are sometimes heard. According to Friedreich,[11] the extra sound may result from the diastolic recoil of the chest wall which has been retracted during systole.

The circumstances under which the physiological third heart sound is generally audible (youthful, physically vigorous subjects) *almost always preclude its interpretation as protodiastolic* gallop rhythm indicating heart failure. However, White states that during the World War a markedly accentuated third heart sound causing protodiastolic gallop rhythm was common in soldiers with neurocirculatory asthenia, a condition in which symptoms simulating those of organic heart disease are common.

Nowadays, the phonocardiogram is often available to aid in the differentiation of gallop rhythm from other forms of triple heart sounds.

PROGNOSTIC SIGNIFICANCE OF GALLOP RHYTHM

Diastolic gallop rhythm is indicative of serious functional impairment of the ventricular myocardium. The presence of diastolic gallop rhythm is, therefore, to be viewed with concern; Thompson and Levine's[33] patients with diastolic gallop rhythm lived an average of only eleven months after it had been discovered. However, in the last analysis, the prognostic significance of a gallop is rationally interpreted only in the light of the underlying cause of the cardiac failure. If the latter is susceptible of improvement, the gallop will clear up with it. Thus, in coronary thrombosis it is common for the patient to recover sufficiently to go about his business despite the fact that following the thrombosis there was a very marked gallop. I have a number of times seen complete recovery in infectious fevers in which severe myocardial damage was revealed by gallop rhythm Despite such cases, however, the appearance of gallop rhythm during pneumonia, typhoid or some other fever is a sign of ill omen. Thompson and Levine[33] observed that 6 patients with gallop rhythm due to rheumatic heart disease lived an average of less than two months after the discovery of the adventitious sound. In acute glomerulonephritis, gallop rhythm is an early indication of beginning insufficiency of the left ventricle, but disappears quickly with restoration of the efficiency of the heart. In

chronic arterial hypertension, gallop rhythm is a most important sign of beginning heart failure and should be sought at each examination. While it is to be taken seriously, such patients may have gallop rhythm, usually faint, for years and still be able to attend to their business. In other hypertensives it comes and goes. Very often, gallop rhythm in hypertensive and arteriosclerotic patients clears up when the cardiac insufficiency is treated successfully by bed rest, appropriate diet, diuretics, and digitalis The same is true of the rare cases in which gallop rhythm is heard in the emphysema heart. It has seemed to me that the louder the gallop sound and the earlier in diastole it occurs, the more serious its prognostic significance.

Systolic Gallop Rhythm.—In this form, described by Potain[26] and Cuffier and Barbillon,[7] the supernumerary sound is between the normal first and second sounds, and generally heard best at the base, most often in the second right interspace Doubt has been cast on the existence of systolic gallop rhythm, but Wolferth and Margolies[33] have recorded it in sound tracings. Systolic gallop is far less common than diastolic gallop rhythm, and the pathogenesis is not clear Potain originally suggested that the extra sound is due to the impact of the blood column in a sclerotic aorta, and this may apply to the cases in which the systolic gallop is heard only in the second right interspace. Thompson and Levine[34] found systolic gallop rhythm of no definite clinical significance, many of their patients were "nervous" people without cardiovascular disease

THE HEART SOUNDS IN CIRCULATORY FAILURE

There may be severe circulatory failure without notable modification of the heart sounds. In other instances, however, circulatory failure is documented by abnormalities in the intensity, pitch or quality of one or the other sound

Feeble ventricular systole tends to be accompanied by a weak first sound and often also, in consequence of the low arterial tension, by a faint second sound. This is well seen in premature contractions and auricular fibrillation, where the beats that are feeble or absent at the wrist have weak sounds Weakness of the sounds of all the beats results from circulatory insufficiency only when the latter is very severe It seems to develop more readily in circulatory failure of peripheral origin (shock) than in heart failure.

In many instances of severe circulatory failure there appears the auscultatory phenomenon known as *fetal rhythm* or *embryocardia*, from the resemblance to the sounds of the fetal heart long ago noted by Stokes[30] in typhus fever with circulatory collapse In fetal rhythm, the sounds are equally spaced as a result of shortening of diastole by tachycardia Further, the first sound is altered in

CHAPTER XXII

MURMURS DUE TO FUNCTIONAL VALVULAR INCOMPETENCE

One of the common consequences of myocardial insufficiency is functional incompetence of one or more valves. The valvular leak may or may not be documented by an audible murmur. The appearance of such a murmur is often an early and valuable sign that the heart is weakening. In many instances the regurgitation is too small to be of significance for the organism as a whole, but in others the functional valvular defect profoundly affects the dynamics of the circulation.

Functional regurgitation may appear in cardiac weakness of any origin. Thus, *it is often seen when the heart dilates in hypertension*, coronary sclerosis, myocarditis, thyroid disease, anemia, defect of another valve, etc. Functional regurgitation is often superadded to an organic valvular defect, though clinically it may be difficult or impossible to differentiate the two components. The relation of the time of appearance of functional regurgitation to the other consequences of myocardial weakness varies. Especially in anemia, murmurs due to functional insufficiency of the valves may appear before there are other notable evidences that the heart is giving way, this phenomenon will be discussed further below.

PATHOGENESIS OF FUNCTIONAL REGURGITATION

The mechanisms through which valvular insufficiency results from myocardial weakness are not entirely clear. However, two factors would seem to be most important:

(*a*) Weakness of the myocardium surrounding the valve ring. There is experimental evidence that the contraction of the myocardium around the auriculo-ventricular orifices plays an important part in their closure. The circumference of the valve orifices is diminished, diaphragm-like, by the systolic contraction of the surrounding heart muscle Roy and Adami[14] long ago found that the circumference of the mitral orifice during systole is only half of that during diastole. According to Lian,[10] while the auriculo-ventricular orifices are circular during diastole, they are transformed into elongated, narrow slits by the systolic contraction. This obviously serves to facilitate the coaptation of the flaps, for the adjacent surfaces are pressed against one another for a longer distance from the free edge than would be the case with a broader ring.

(*b*) Displacement of the attachment of the papillary muscles When the ventricle dilates, the attachments of the papillary muscles are moved further from one another and from the valve flaps This also interferes with the proper closure of the valves, though it is compensated to a greater or less extent by the elongation of the papillary muscles which is part of the dilatation, and sometimes also by elongation of the chordæ tendinæ It is also conceivable—though I know of no proof that this actually occurs—that such an elongated and frequently degenerated papillary muscle may be unable to maintain the valve flap against the systolic intraventricular pressure with resultant eversion of the edge into the auricle and regurgitation In this connection, it should be remembered that degeneration and fibrosis of the papillary muscle is often a relatively early occurrence in arteriosclerotic heart disease Moreover, the systolic intraventricular pressure rises abnormally high in hypertension and some varieties of valvular disease.

In addition to these muscular factors in the causation of relative insufficiency, Sprague[17] emphasizes the importance of certain mechanical forces He points out that forces entrained by a forceful jet passing through a valve and especially the region of negative pressure following the abrupt cessation of the jet participate in perfect coaptation of the valve segments It seems likely (*cf* Sprague's excellent discussion), though not proved, that inadequate discharge through a valve due to heart failure may favor imperfect closure.

Direct evidence that dilatation of the ventricle produces functional valvular insufficiency with a systolic murmur has been obtained by Lian.[9] He produced dilatation of the ventricles in dogs by means of asphyxia. As the ventricles dilated, systolic regurgitation into the auricles was observed and an apical systolic murmur was heard. The regurgitation and murmur disappeared with the dilatation when the asphyxia was alleviated.

Certain of the facts brought out by Kirch (page 298) regarding the anatomy of ventricular dilatation are of importance in connection with the production of functional valvular incompetence He found that dilatation of the left ventricle in hypertension and aortic valvular disease is initiated in the outflow tract, especially in its apical portion, producing lengthening but little broadening of the ventricle. The result is that at this stage of dilatation, the mitral orifice is unaffected. It is only at a later stage, when the dilatation also involves the inflow tract, that the muscle surrounding the mitral orifice becomes likewise implicated and functional insufficiency appears This is the stage in which the transverse diameter of the ventricle, in addition to the previously affected longitudinal diameter, becomes increased, *i e.*, when the heart is broadened as well as lengthened. Similar considerations apply to the right

ventricle and the tricuspid orifices. Kirch also found that when the dilatation of the heart is purely a result of increased work and not due to disease of the muscle (so-called tonogenous dilatation), the dilatation consists only in enlargement of the outflow tract with elongation of the heart; the inflow tract is unaffected and the transverse diameter of the heart little affected. The result is that in this form of dilatation functional insufficiency of the auriculo-ventricular valves does not appear. On the other hand, when disease of the muscle participates in the production of the dilatation (myogenous dilatation), Kirch found that the inflow tract is involved and the heart broadened, with the result that functional regurgitation develops in the auriculo-ventricular valves. The early appearance of functional regurgitation in cardiac dilatation due to myocarditis or anemia is thus readily comprehensible.

FUNCTIONAL MITRAL REGURGITATION

This may develop in dilatation of the left ventricle of any origin. Thus, functional mitral incompetency is encountered when the heart gives way in hypertension, aortic valvular defects and coronary sclerosis, as well as in the myocarditides, various fevers, anemia, thyrotoxicosis, etc. With restoration of the functional capacity of the left ventricle, disappearance of the systolic murmur often indicates that the regurgitation has ceased. Transitory functional incompetency occurs in paroxysmal hypertension and is common in episodes of cardiac asthma.

It would appear probable that functional regurgitation due to ventricular dilatation is often superimposed on organic lesions of the mitral valve. Indeed, in all likelihood the apical systolic murmur in early rheumatic fever is largely, if not entirely, due to disease of the ventricular myocardium, and not to the minute verrucæ which are present on the mitral valve at this stage.

In other cases, functional regurgitation is uncomplicated by organic changes in the valve apparatus. There can be little doubt that this is the case in the transitory mitral regurgitation of paroxysmal left ventricular failure in hypertension, aortic insufficiency, etc. And in many long-standing systolic murmurs in hypertension, syphilitic aortic insufficiency, etc., I have satisfied myself at necropsy that the circumference of the mitral orifice was not above the normal.* This indicates that the insufficiency must have been due

* The demonstration of functional or lesser degrees of organic mitral insufficiency at necropsy is difficult King[8] long ago observed that in some healthy hearts water introduced into the left ventricle is retained by the mitral valve, but in others there is regurgitation into the auricle More recently, Lian[19] has found that when water is introduced into the left ventricle and the latter compressed, there is always a flow through the mitral valve However, by using a standard pressure, he has been able to detect small leaks by the accelerated flow through the orifice

to the purely functional causes mentioned above. But there are also cases of functional mitral incompetence of protracted duration in which the mitral orifice is found at necropsy to be dilated. Evidently, in these instances the mitral ring has finally become stretched perhaps largely as a result of the loss of the muscular support which is so important in the normal functioning of the mechanism Here, the organic changes are secondary to the functional derangement. In many, though by no means all, instances of so-called arteriosclerotic mitral insufficiency, the valvular incompetence seems to be the result of such stretching of the ring secondary to the muscular dilatation, and not to the few atheromatous foci on the curtains.

The traditional physical sign of functional mitral insufficiency is an apical systolic murmur, transmitted more or less well toward the left axilla and sometimes even to the back. Most often, the murmur is rather soft, but it may also be loud It is not accompanied by a thrill. Usually, the murmur occupies only the first part of systole but it may extend almost to the second sound There is nothing characteristic about the effect of position on the murmur It is thus evident that the characteristics of the murmur do not serve to differentiate it from that of organic mitral disease, except that a rough murmur accompanied by a thrill is not purely functional. The differentiation between functional and organic systolic murmurs must be made almost entirely on the basis of the accompanying circumstances. If the appearance of the murmur accompanies the onset of left ventricular failure, it is almost surely functional; this opinion is substantiated if the murmur disappears as the heart rallies Cardiorespiratory murmurs, if apical, can generally be differentiated from that of functional mitral insufficiency by the characteristic change with the phase of respiration.

It should be mentioned that there are many instances of left ventricular failure with characteristic clinical pictures in which no apical systolic murmur is audible. I do not known whether this indicates that, for some obscure reason, the murmur is not sufficiently well transmitted to be audible. With extremely wide mitral insufficiency it is, of course, not surprising that the murmur may be absent Nor is it known whether the development of functional mitral insufficiency is a necessary prerequisite for the clinical picture of left ventricular failure The latter is usually dominated by the consequences of pulmonary engorgement (page 426). It is to be presumed that high tension in the pulmonary circuit may be solely a consequence of the impediment to ventricular filling offered by the elevated diastolic intraventricular pressure that is part and parcel of the failure of the ventricle, and that systolic mitral regurgitation is merely an accessory and unessential factor. Of course, once systolic regurgitation is present it will contribute greatly to the hypertension of the lesser circulation

FUNCTIONAL TRICUSPID INSUFFICIENCY

The structure of the tricuspid valve is such that the total area of the curtains is but little in excess of that of the orifice. Anatomical considerations thus indicate that appropriate diminution in the size of the tricuspid orifice by muscular contraction must be very important for the function of the valve, and that incompetence may arise quite readily. Indeed, King[5] showed long ago that when the right ventricle is filled with water soon after death, there is always a very considerable regurgitation into the right auricle. He considered that this physiological incompetency subserves a useful function in averting pulmonary engorgement when the venous return to the right heart is unduly accelerated, and termed it the "safety-valve function of the right ventricle."

It is therefore not surprising that functional incompetence of the tricuspid valve often becomes very marked when the right ventricle is dilated. A tricuspid leak may develop in right heart failure of any origin, the most common varieties are those secondary to mitral, aortic, arteriosclerotic and hypertensive disease affecting primarily the left heart, and the right ventricular failure of emphysema and other conditions marked by increased tension in the pulmonary circuit. The pathogenesis of relative tricuspid incompetence is analogous to that of relative mitral insufficiency, which has already been discussed. In some instances of undoubted functional tricuspid insufficiency, as is true of similar mitral defects, the orifice does not appear enlarged at necropsy, the regurgitation having apparently been a direct consequence of myocardial weakness. But in others the ring is dilated to well above its normal circumference of 12 or 13 cm., readily admitting four or more fingers.

Current clinical opinion often contains the tacit assumption that relative tricuspid incompetence is always present when right heart failure is revealed by such peripheral manifestations as engorgement of the veins and liver. While this may be true, it has not been proved to be the case. In many instances of right heart failure, graphic study of the pulsations in the cervical veins and of the enlarged liver reveals no unequivocal evidence of tricuspid regurgitation. Of course, tricuspid regurgitation can and does exist without such evidence. However, it may well be, as discussed in connection with functional mitral insufficiency, that the venous engorgement of right heart failure can result purely from the increased diastolic tension in the right ventricle without preternatural regurgitation through the valves. The question is theoretically important and in need of further study.

The recognition of relative tricuspid insufficiency is by no means always easy. The typical systolic murmur is located in the fourth and fifth interspaces close to the left of the sternum and is trans-

mitted better to the right than the left. It is usually rather soft, and is not accompanied by a thrill. In cases in which such a murmur is known not to have been present, its appearance may characterize quite definitely the complication by tricuspid competency of mitral or other cardiac disease Often, however, the murmur is difficult to separate from the mitral systolic murmur that is usually also present. In fact, Laubry[7] holds that many systolic murmurs believed to be of tricuspid origin are actually mitral murmurs, the site of maximum loudness of which has been displaced toward the mid-line by rotation of the heart due to dilatation of the left ventricle. The murmur should not be confused with the not uncommon crunching sound due to movement of the xiphoid. There are many cases of relative tricuspid insufficiency in which a murmur is not audible And in extreme, usually terminal, weakness of the right ventricle, a previously distinct murmur may weaken or become inaudible.

A sign that may awaken the suspicion of tricuspid insufficiency at the first glance is the *ventricular form of venous pulse* in the cervical veins, *i. e.*, that form of the venous pulse which is dominated by a large systolic filling of the vessel This phenomenon is described on page 117, where it is pointed out that it also occurs in auricular fibrillation in the absence of marked tricuspid insufficiency The simultaneous presence of auricular fibrillation and tricuspid insufficiency, for reasons mentioned on page 117, offers the ideal condition for the development of a prominent ventricular venous pulse In the many instances in which the ventricular venous pulse can be seen in the veins of the extremities (page 118), there is probably almost always tricuspid insufficiency It should be mentioned that tricuspid insufficiency is present on unusual occasions in the absence of ventricular venous pulse, this is most likely due, as pointed out by Mackenzie,[12] to the presence of a very capacious auricle which takes up the regurgitated blood with little increment in intra-auricular tension and consequently but slight transmission of a wave into the jugulars Unusually efficient valves in the lower ends of the jugular veins may also be concerned

Rapid filling from below of the jugular veins which have previously been emptied and compressed by the finger, has been thought evidence of tricuspid insufficiency. However, this may also result from auricular engorgement of any origin, notably in auricular fibrillation.

An almost unequivocal sign of tricuspid regurgitation, when present, is systolic pulsation of the liver (page 256). However, it is not demonstrable by physical, or even by graphic, examination in all instances of tricuspid incompetency. This is probably often due to the same causes as those just mentioned which prevent the appearance of the ventricular form of the venous pulse in the cervi-

cal veins. In long-standing tricuspid disease, induration of the liver may inhibit hepatic pulsation. There are many instances of tricuspid insufficiency in which a ventricular venous pulse in the cervical veins is not accompanied by hepatic pulsation, presumably because the regurgitation is not forcible enough to distend the liver sufficiently for palpation.

The symptoms in relative tricuspid insufficiency are those of right heart failure in general, which may of course be superimposed on those of left-sided failure. It will bear repetition that with the onset of relative tricuspid regurgitation orthopnea and other symptoms due to the pulmonary engorgement of left-sided failure may be greatly ameliorated while the evidences of systemic venous engorgement are aggravated

FUNCTIONAL AORTIC INSUFFICIENCY

When water is introduced under high pressure into the aorta or pulmonary artery at postmortem examination, only a minute quantity passes through the healthy valve into the corresponding ventricle The factor of muscular contraction thus appears to be of far less moment for the closure of the semilunar valves than for that of the auriculo-ventricular aperture In accord with this, functional insufficiency of the arterial orifices would be anticipated to be much less common than is true of the auriculo-ventricular valves. In fact, the existence of functional insufficiency of the semilunar valves was long denied by many clinicians. Of course, relative insufficiency of the aortic orifice due to permanent dilatation of the aortic ring as a part of a dilatation of the aorta, already known to Corrigan,[2] is not to be included in the category of functional aortic insufficiency Bearing this distinction in mind, functional aortic insufficiency is quite unusual, but does occur Cases which exhibited an aortic diastolic murmur and the characteristic peripheral phenomena of aortic regurgitation but in which the aortic valve was normal at necropsy (even holding back water as well as normally) have been reported by Laubry and Doumer[9] (4 cases), Schlesinger,[16] and many others.

True functional aortic regurgitation is a complication of dilatation of the left ventricle Why it is present in rare instances of such dilatation, and is absent in the vast majority, is not clear. Presumably, functional regurgitation develops when the dilatation involves the myocardium immediately connected with the aortic ring; evidence for this conception is afforded by the observations of Ortner, mentioned below. The rarity of functional aortic regurgitation is the more peculiar in the light of the observations (page 298) that dilatation of the left ventricle in hypertension is initiated in the terminal portion of the outflow tract.

Two main groups of cases of functional aortic insufficiency are encountered:

1. Those in which dilatation of the left ventricle accompanies arterial hypertension In these instances there is apparently coincidence of the two factors of dilatation of the heart muscle and stretching of the aortic ring by the high blood pressure. Gallavardin and Vaquez[3] have noted transitory aortic incompetence during hypertensive crises, which disappeared when the blood pressure fell. I have on several occasions observed the development of the typical murmur of aortic insufficiency during the last days of life of patients with hypertension and left ventricular failure which exhibited the murmur of aortic incompetence with the characteristic peripheral phenomena, and in which the aortic valves were normal at necropsy.

2 In the course of pernicious anemia, as was observed by Biermer[1] in his original cases, the characteristic diastolic murmur of aortic insufficiency may develop. According to Goldstein and Boas,[4] prior to the introduction of the liver treatment, about 10 per cent of patients with pernicious anemia exhibited such murmurs, they may also develop in severe secondary anemia At postmortem examination, the aortic valves may show no abnormality In two cases of pernicious anemia with functional aortic insufficiency, Ortner[13] made the interesting observation that "precisely that portion of the heart muscle which serves as a support of the aortic valve was the seat of fatty degeneration of very high degree, while the rest of the heart muscle showed this degenerative change to a much less extent" This localization perhaps accounts for the fact that the patients may have few symptoms of heart failure

Functional aortic insufficiency may also develop in left ventricular dilatation of other origin, thus, Laubry and Doumer[8] verified the existence of such a functional aortic murmur at the necropsy of a case of adhesive mediastino-pericarditis

FUNCTIONAL INSUFFICIENCY OF THE PULMONIC VALVE

Like the corresponding aortic defect, this is unusual though not as rare as has been generally thought. Relative insufficiency of the pulmonic valve was observed by Stokes[19] and his contemporaries, but the attention of the profession to the question of functional pulmonic regurgitation is largely due to the description by Steell[18] of a diastolic murmur of high pressure in the pulmonary artery, since known as the Graham Steell murmur. There has been considerable discussion *pro* and *con* relating to the existing of such a murmur of functional pulmonic insufficiency, but sufficient material with necropsy control has now been reported to state that such murmurs are not great rarities, I have encountered them several times

Functional pulmonic insufficiency occurs most often in mitral stenosis, but may also complicate on rare occasions the other conditions which lead to hypertension of the lesser circulation, *e. g.*, emphysema, extensive pulmonary fibrosis, kyphoscoliosis, etc. (See Schwartz[15] for literature) I saw a case of left ventricular failure in hypertension in which a murmur of pulmonic regurgitation developed; but here the necropsy revealed a bicuspid valve, an anomaly which doubtless predisposed the valve to incompetency when under the strain of the increased tension in the pulmonary circuit.

At necropsy, most of the cases reveal widening of the pulmonic ring accompanying dilatation of the pulmonary artery and conus arteriosus of the right ventricle. It would seem that the most important factor in the production of the dilatation of the ring is the increased pressure in the pulmonic circuit, *i. e.*, the defect is basically functional in causation. However, in the cases of mitral stenosis, further study is needed to learn what part is played by involvement of the pulmonic ring by the rheumatic lesions which Kugel and Epstein[6] have shown to be so common in the pulmonary artery proper, especially at the root. It is also possible that there are cases in which an atherosclerotic process in the pulmonary artery implicates the ring. Notable atherosclerotic lesions of the cusps themselves must be rare, if they occur at all.

The regurgitation results in a diastolic murmur. It is heard best in the second and third interspaces to the left of the sternum and may extend a variable distance downward or to the left. The murmur is generally soft and faint; it follows directly after the second sound and is of variable length Obviously, these characteristics do not serve to differentiate the Graham Steell murmur from that of aortic insufficiency. The differentiation has been considered so difficult that many clinicians refuse to make a diagnosis of functional pulmonic insufficiency under any circumstances. However, there are cases in which the diagnosis may be ventured with considerable assurance It is based on the absence of indications of aortic insufficiency other than the murmur and the presence of a cause (usually mitral stenosis) for, and evidences of, hypertension of the lesser circulation. The latter are:

1. Very marked accentuation of the pulmonic second sound, usually accompanied by a palpable impulse in the pulmonic area.

2. Roentgenological evidence of dilatation of the pulmonary artery. The following excellent description is given by Schwartz.[15]

"Fluoroscopically, cases with mitral stenosis when placed in the right anterior oblique position show as a characteristic sign of the disease a marked encroachment of the left auricle upon the retrocardiac space. This is true also in cases in which there has been an accompanying mitral insufficiency of long duration so as to cause left ventricular hypertrophy

With the patient in the same position, there is only moderate bulging of the pulmonary artery visible in the uppermost part of the cardiac shadow toward the anterior part of the chest. In the cases of mitral stenosis, however, which present a diastolic murmur at the second or third intercostal spaces to the left of the sternum (in the absence of signs of aortic disease), the pulmonary artery almost assumes the first upper curve of the left side of the heart in the form of a huge bulge which shows just as prominently in the right anterior oblique position. The artery does not pulsate forcibly as in congenital lesions of the heart (there may be a 'hilar dance,' see page 218) When the left ventricle is not markedly enlarged this pulmonic bulge may also be seen in the uppermost space adjacent to the spinal column with the patient in the left posterior oblique position . . I have never observed a similar dilatation of the pulmonary artery in cases of mitral stenosis accompanied by aortic insufficiency " In some of the cases, a small left ventricle speaks strongly against aortic insufficiency

3 Right axis deviation in the electrocardiogram.

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CHAPTER XXIII

CARDIAC PAIN*

PAIN may be a symptom of any of the diseases marked by structural changes in the heart, although the frequency and severity of the pain varies enormously in the individual affections. Pain having at least some characteristics in common with that of "organic" heart disease is also common in neurocirculatory asthenia and other neuroses And finally the same sort of pain may appear in the healthy as a result of great overexertion, as in athletics for which the individual is not properly trained. In all of these circumstances there is reason to believe that the pain is the result of stimuli acting on the sensory nerves within the heart. However, it may well be that in addition to those conditions in which actual changes in the heart result in preternatural stimulation of the nerve endings, pain may also result, in neurocirculatory asthenia, from the wonted stimuli acting on a hypersensitive nervous apparatus. In the following we shall use the term *cardiac pain* as a generic designation for pain mediated through the cardiac nerves, whatever the pathogenesis and whether it is localized in the immediate vicinity of the heart or is referred to such parts as the elbow or the abdomen.†

* For a detailed discussion of cardiac pain and the physiology and pathology of the coronary arteries, the reader is referred to Levy's[26] authoritative work

† In connection with terminology, a few words may not be amiss regarding the term *angina pectoris*, which has been used with various connotations and thus led to confusion Heberden[15] originally introduced the expression to designate a disease, or, as he put it, "a disorder of the breast marked with strong and peculiar symptoms" Heberden's patients were probably almost all sufferers from coronary arteriosclerosis although some may have had syphilitic aortitis. Consequently, many physicians use the term angina pectoris, or Heberden's angina, to connote a *disease* in which there is narrowing of the coronary arteries However, such a usage seems ill-advised, for in many instances of the diseases (coronary arteriosclerosis and syphilitic aortitis) in which there is narrowing of the coronary lumens, the clinical picture is dominated by heart failure and pain is entirely absent, so that the designation angina pectoris is out of place The tendency of contemporary writers is to use angina pectoris as a designation of a *symptom*, and when possible to qualify it by the cause, *e g*, angina pectoris due to coronary arteriosclerosis, to syphilitic aortitis, or to rheumatic aortic regurgitation Thus, in a recent lecture, Libman[23] defines angina pectoris as "a term used to describe a pain and certain accompanying clinical phenomena, of a kind that lead one to believe that the causation lies in the cardiovascular apparatus of the thorax, this including the heart, blood vessels and nerves" Used in this sense, which seems the best justified and which will be applied in this book, *angina pectoris becomes little more than a synonym for cardiac pain* The conception of angina pectoris will be more sharply defined if it is proved, as recent investigations to be summarized in the following strongly indicate, that the pain in question is practically always a manifestation of myocardial ischemia Great circumspection is needed in the use before patients of the words angina pectoris, for they have become almost synonymous with sudden death in the lay mind In all probability the term angina pectoris will gradually become obsolete in other than historical discussions, to be replaced by expressions such as cardiac pain due to coronary arteriosclerosis, aortic regurgitation, etc.

Discussion of the occurrence of cardiac pain (for statistics see Bruenn, Turner and Levy[4]) will be postponed to the sections on individual diseases. Here, it may be remarked that the classical domain of cardiac pain is narrowing of the coronary lumens due to arteriosclerosis, thrombosis, or syphilis. Pain is also common and severe in aortic valvular disease, but far less frequent in pronounced form in mitral and other valvular defects. In right-sided cardiac strain secondary to pulmonary lesions or congenital heart disease the so-called angina hypercyanotica (page 544) occurs on rare occasions In rheumatic, diphtheritic, and other forms of myocarditis, and in acute and subacute bacterial endocarditis, precordial ache is occasionally present but severe pain is a rarity, if it occurs in uncomplicated cases In massive cardiac hypertrophy due to hypertension or mediastino-pericarditis, cardiac pain occurs but is rarely severe in the absence of complicating coronary artery disease. On rare occasions, the inception of a new rhythm, as auricular fibrillation or paroxysmal tachycardia, is accompanied by violent anginal pain; the picture may simulate coronary thrombosis. Most instances of pericarditis are painless, but sometimes pain does occur. Typical cardiac pain may result from anemia It may also be a symptom in the overacting heart of hyperthyroidism or when thyroid is administered in myxedema. Finally, it may be repeated that cardiac pain is a common symptom of neurocirculatory asthenia and may occur in the healthy during violent exertion

CHARACTERISTICS OF CARDIAC PAIN

In its most typical form, cardiac pain occurs in paroxysms precipitated by exertion, is located under the sternum with a tendency to radiate to the left shoulder, is compounded with a sense of constriction, and is relieved by rest or nitrites. But none of these characteristics is constant and they are combined with one another or additional manifestations in almost infinite variety

The attack is brought on by exertion or excitement (angina of effort); the one concerned is largely determined by the habits and temperament of the patient. In cases in which exertion produce pain, Wayne and Laplace[49] found with a stair-climbing test that the amount of exercise required to evoke pain was approximately the same on repeated examinations of any individual A hearty meal may be followed by pain, as may exposure to cold; victims of coronary arteriosclerosis often have less pain in Florida than in New York during the winter Exercise following a full meal or in the cold is especially apt to incite cardiac pain in those subject to it. Less often cardiac pain appears in the absence of any obvious exciting cause, even when the subject is asleep—the *angine de décubitus* of Vaquez[45] Such nocturnal attacks are especially apt

to occur in individuals who also have cardiac asthma, with which they may alternate. Remarkably enough, in rheumatic aortic regurgitation anginal pain may not only appear when the individual is at rest but also be relieved by getting up and walking about (page 475).

The *site* of the pain is most often under the sternum, reaching rather more to the left than to the right. Less often it is situated toward the apex of the heart, a site which is more common in pains of psychoneurotic origin. While the pain may remain strictly localized in the substernal or precordial region, when severe it tends to radiate toward the left shoulder and down the left arm. Most often radiation is down the inner surface of the left arm as far as the elbow, but it may also extend down to the little and ring fingers. Radiation to the corresponding points of the right side occurs but is less common. Not rarely, the pain extends to the back, especially to the interscapular region. Sometimes, especially in coronary thrombosis, the pain is referred to the epigastrium. Exceptionally, the pain extends to the jaw, teeth or head; teeth have been extracted for pain of cardiac origin Radiation of the pain to the left testicle and lower extremity has been described. I recently saw a case of coronary thrombosis in which the pain, accompanied by cutaneous hyperalgesia, involved the entire left half of the body.

It is to be emphasized that there are many instances in which cardiac pain is referred entirely to the shoulders or less often the elbows or other parts of the upper extremities, especially the left. Libman[28] long ago discussed the association of the symptomatology of disease of the shoulder joint or subacromial bursa with angina pectoris Howard[18] described periarthritis of the shoulder with coronary artery disease. I have repeatedly known individuals with coronary arteriosclerosis to be regarded as suffering from arthritis of the shoulder-joint or subacromial or subdeltoid bursitis for considerable periods Edeiken and Wolferth[7] have recently described 14 cases in which more or less constant pain in the shoulder region, most often the left but also the right, developed within a period of four months after acute myocardial infarction; they observed the pain to last over five years Dr E P Boas and the writer have made similar observations and the subject has been discussed *in extenso* by Boas and Levy.[3] We have also obtained a history of shoulder pain of duration of even a year preceding coronary thrombosis, many of the patients had marked limitation of movement and were treated for arthritis of the shoulder or subacromial bursitis The frequency with which cardiac pain first manifests itself exclusively in the shoulder is so great that the practitioner should bear the possibility in mind in all middle-aged individuals who complain of pain and limitation of movement in the shoulder, especially the left. Edeiken and Wolferth regard the pain as analogous to causalgia; they quote Leriche as finding that obstruction of an artery may produce causalgia. However, the fact that the pain may precede coronary thrombosis would speak against the validity of this explanation in all cases. Perhaps reflex hypertonus of the muscles of the shoulder girdle plays some part, the joint and adjacent bursæ being damaged as are the joints of a hemiplegic limb

Anginal pain is occasionally referred to a diseased viscus, such as a carious

tooth (Mackenzie[31]) or a diseased gall-bladder. On the other hand, Boas and Levy[2] point out that in patients with coronary artery disease pain emanating from peptic ulcer or a diseased gall-bladder may be referred to the usual distribution of cardiac pain These interrelationships, which may produce diagnostic dilemmas, are perhaps attributable to sensitization of spinal segments corresponding to the diseased viscera (cf Boas and Levy for an excellent discussion).

The nerve pathways concerned in the reference and radiation of pain from the heart are discussed on pages 420 and 775.

The pain is variously pictured Most often it is described as pressing, gripping, constricting or vise-like in character, or as a feeling of tightness across the chest or strangulation. The feeling of constriction may be in the neck and may then be difficult to differentiate from dyspnea Mackenzie[30] attributes the sensation of constriction to reflex hypertonus of the intercostal muscles, a conception which is not proved The pain is continuous and not throbbing. The pain may be burning Sometimes it is described as a feeling of weight under the sternum which is more oppression than actual pain. Often the patient depicts his discomfort as a feeling of gaseous distention behind the lower sternum or in the epigastrium, and states that he is relieved when he belches. According to Mackenzie, this is due to swallowing of air during the pain, which is brought up when the pain is relieved Although the skin may be hyperesthetic, cardiac pain is neither produced nor intensified by pressure. In the arms or hands the sensation is often that of numbness, weakness, tingling, or burning, these may antedate actual pain

The intensity and duration of the pain vary within wide limits All gradations between trivial and momentary retrosternal oppression and protracted constriction so agonizing that the victim remains, whatever his position, as though held in a vise. Any attack lasting an hour or more is suspicious of coronary thrombosis, in the latter the pain may last for days or even weeks and be controllable only by heroic doses of morphine. The subject usually prefers to remain quiet until the storm has passed or been relieved by medication, but, as mentioned above, there are cases, especially in aortic regurgitation, in which relief is obtained by moving about

Libman[29] has emphasized that cardiac pain is to be interpreted in the light of the individual's sensitivity to pain He has found that attacks of coronary thrombosis with little or no pain, but with such manifestations as weakness, syncope, vomiting, sweating, and other manifestations of shock, are especially apt to occur in those who give other evidences of hyposensitivity to pain * Some of the cases of what Gairdner[9] called *angina sine dolore*—in which these manifestations may be accompanied by peculiar sensations in the cardiac region that the patient finds it difficult to describe

* And when pain does occur in such hyposensitives, Libman finds that it is apt to be atypical in location and radiation

but are not actual pain and by fear of impending death—doubtless belong in this category. However, Wayne and Graybiel[48] point out that this picture may also result from the onset of an abnormal rhythm (approaching ventricular fibrillation in their case). Conceivably, though this is only a hypothesis, the abnormal rhythm is engendered by myocardial ischemia in an area in which the nerves have previously been damaged and do not transmit the pain impulses, so that the attack is similar in pathogenesis to cardiac pain

Attacks of angina pectoris may include a fear of impending death, the well-known *angor animi* or fear of impending dissolution. However, this is present in only a minority of even severe paroxysms, and is doubtless often a result of the patient's knowledge of the dangers of his condition.

Cardiac pain is often accompanied by tenderness of the skin and muscles of the affected area. Often, indeed, the hyperalgesia extends considerably beyond the limits of the pain, even down to the little finger of the left hand, and may be continuously present for months even though there are few painful seizures. In attacks of coronary thrombosis with little or no pain precordial hyperalgesia may be present Various reflex phenomena may occur. Thus, I saw a patient in whom the attacks were accompanied by blanching of the little finger of the left hand due to vasoconstriction and another in whom the entire left hand was blanched. There may be spasm of the muscles of the shoulder girdle. Sweating and salivation are common, and the seizure may be followed by the passage of large volumes of pale urine. On very rare occasions herpes zoster implicates an area closely associated with the distribution of the pain; Spillane and White[41] suggest that "repeated bombardment of spinal root ganglia by afferent impulses from the ischemic heart gives rise to antidromic impulses that lead to vasodilatation and blister formation in referred cutaneous areas." Some patients are pale during the attack, others flushed.

Respiration is not always affected during cardiac pain. When the pain is very severe, the patient may hold his breath for a long period and then state that he could not breathe. Heberden originally described dyspnea as absent during the seizure, and this is most often true. Often, however, the patient states he cannot catch his breath during the attack. Anginal attacks awakening the patient from sleep may be associated with paroxysmal dyspnea (cardiac asthma) and be repeatedly accompanied by pulmonary edema. In such instances, presumably, either a disturbance in the circulation of the left ventricle not only evokes the pain but also failure of that chamber, or else some factor increasing the work of the left ventricle (*e g.*, a disturbing dream) produces both the pain and the failure. Often it is difficult to differentiate whether a sensation of strangulation or thoracic oppression is pain or dyspnea.

In attacks of cardiac pain not due to coronary thrombosis,

arterial pressure is almost always elevated, though rarely much, over the level prevailing in the intervals. This was the case as regards the systolic pressure in 13 of 15 patients studied by Wood and Wolferth[53] and in all 23 observed by Levine and Ernstene.[24] The diastolic pressure generally shows little change. A sharp fall in arterial pressure during cardiac pain or after it is strongly suggestive of coronary thrombosis, it also often occurs when the pain accompanies the onset of an ectopic rhythm. In partial and complete coronary obstruction in anesthetized animals Sutton and Lueth[44] and Wood and Wolferth always observed a fall in arterial pressure In unanesthetized animals, Shambaugh[38] found that coronary obstruction was followed either by a fall or less often a slight rise in pressure. Wood and Wolferth attribute the rise in pressure dur ng anginal pain to pressor reflexes evoked by the pain On the other hand, Levine and Ernstene and Wayne and Laplace believe the rise in pressure to be rather one of the causes than a consequence of the anginal seizure The latter investigators base this opinion on the observation, in individuals in whom they produced cardiac pain by exercise, that a rise in pressure equal to that observed during the pain was produced when they stopped the exercise just short of provoking pain

The state of the *pulse* during the attack is largely dependent on the underlying condition and on the exercise, excitement or other factors which precipitated the seizure. Often, as described by Heberden, there is no change in the pulse during the attack Goldhammer and Scherf[12] detected ventricular extrasystoles during attacks, attributing them to the ischemic focus. In 4 of their 11 patients, Wayne and Laplace observed alternation of the pulse during anginal attacks brought on by exercise, but alternation can often be evoked by exercise when the heart is diseased (page 85) in the absence of pain

THE NATURE OF CARDIAC PAIN

Cardiac pain stands almost alone among symptoms in the speculation it has provoked; Huchard[19] enumerated no less than eighty theories of the origin of angina pectoris. We shall not review these theories but refer the reader to the great works of Allbutt[1] and Huchard for their details, and to the paper of Keefer and Resnik[21] *for an excellent* and more recent survey which forcibly impressed on the profession the strength of the evidence for the anoxemia theory of angina pain Omission of a historical discussion (see Herrick[17]) is all the more permissible since the theory that the common forms of severe cardiac pain are due to ischemia of the myocardium—evolved by Heberden's contemporaries, Hunter, Jenner, Parry, and Burns on the basis of the detection of calcification ("ossification")

of the coronary arteries at necropsy in individuals who had angina pectoris—seems, after a century and a half of vicissitudes in favor, finally to have been established by experimental study. The conception was formulated in very much its modern form by Burns[4] He held that angina pectoris arises from deficient blood supply to the myocardium due to coronary narrowing, much as pain quickly develops when one attempts to exercise an extremity about which there is a constricting band.

Cardiac Pain and Myocardial Ischemia.—The evidence establishing Burns' theory that myocardial ischemia produces cardiac pain is as follows

1 In the vast majority of instances of severe cardiac pain one finds at necropsy narrowing of the coronary arteries, either along the trunks as a result of arteriosclerosis or at their mouths in consequence of syphilitic aortitis. Most of the remainder have free aortic regurgitation, which diminishes coronary flow (page 475). It will be seen later that in at least some of the few remaining causes of severe cardiac pain—other than those of psychoneurotic origin—factors are operative which may interfere with the metabolic exchanges between blood and heart muscle.

2. Coronary thrombosis (and the rare embolism or occlusion of the coronary mouths by aortic vegetations) results in violent cardiac pain, fundamentally similar to that in the class of cases just described. That the pain of coronary occlusion is due to localized myocardial ischemia would seem highly probable.

3. During paroxysms of cardiac pain electrocardiographic changes have been observed which are of the same type as those occurring in coronary thrombosis and which pass away with the pain. The first observation of this nature was made by Bousfield[3] in a patient with aortic regurgitation and a history of both rheumatic fever and lues As he was about to take the record spontaneous cardiac pain appeared and the electrocardiogram (previously abnormal) showed changes akin to those of the common type of bundle-branch block, and then reverted, with the passing of the pain, to its previous form. Similar observations of electrocardiographic changes during anginal pain have been made by Feil and Siegel[8] and others. Wood and Wolferth studied 30 patients with angina pectoris; in 6 the attacks observed were spontaneous, in the remaining 24 they were induced by exercise. In 15 of the patients the attacks were accompanied by transitory inversion of the T wave, deepening of an already inverted T wave, or deviation of the R–T segment from the base line; none of these changes occurred during exercise in control subjects, with or without cardiac disease, who did not have anginal pain. Wood and Wolferth were able to produce similar changes in the electrocardiogram of dogs and cats by temporary interference with the coronary circulation. Finally, Larsen[23] observed the same

changes in the electrocardiogram in 13 of 17 patients with coronary disease during induced anoxemia. The demonstration that in angina pectoris due to coronary arteriosclerosis or aortic regurgitation transitory changes occur in the electrocardiogram of the same type as in coronary thrombosis, experimental coronary obstruction, and induced anoxemia, furnishes strong evidence of circumscribed myocardial ischemia during the attack.

4. Recently, what appears to be cardiac pain has been produced in animals by temporary obstruction of the coronary arteries. A great difficulty in the study of angina pectoris in the experimental animal has been that the subjective nature of the basic phenomena of the attack renders them difficult to register in animals. However, this has been overcome to some extent by experiments of Singer,[39] Sutton and King,[43] and Sutton and Lueth The latter investigators passed a ligature around a large coronary branch in the dog. When the artery was narrowed or occluded by traction on the ligature the dog always manifested pain by restlessness, stiffening of both forelegs, but especially the left, limping of the left foreleg, and whining With release of the ligature, the evidences of pain promptly subsided. Sutton and Lueth believe that the pain is conducted by nerve fibers around the blood vessels for the pain disappeared when the arterial wall was stripped and painted with 80 per cent alcohol They further found that occlusion of a coronary mouth by a small knob at the end of a brass rod produced pain. This indicates that the pain called forth by occlusion with a ligature is actually due to diminution in blood flow to the myocardium and not to pressure on the nerves or to distention of the artery above the ligature.

Using Sutton and Lueth's technic, Pearcy *et al.*,[33] White *et al.*,[52] Katz *et al.*,[34] and Shambaugh[18] have been able to evoke the same pain responses in the dog Nevertheless, Katz and his associates do not believe that the pain is due to the occlusion of the coronary artery and the resultant myocardial ischemia, but rather that it results from direct stimulation of the nerve plexus surrounding the artery. They base this view on observations that compression of a carefully isolated coronary artery produced no pain, although the latter developed when the undissected artery above or below the occlusion of the carefully isolated artery produced no pain, the ligature was compressed; and that while complete preliminary latter could still be evoked by compression of the artery above or below the site of occlusion. However, it seems difficult to explain other than on a basis of myocardial ischemia, Sutton and Lueth's finding that plugging of a coronary mouth produces pain, and Shambaugh's recent demonstration that if slight compression insufficient to produce pain be maintained and then the work of the heart be increased by the injection of epinephrin, pain results

5. The fact that any agent which increases the work of the heart and consequently the requisite volume of coronary blood flow may precipitate cardiac pain is in excellent accord with the theory that the pain is due to ischemia of the muscle. Among these agents are:

(*a*) Exercise and excitement are the common incitants of anginal attacks. They not only increase the minute volume and blood pressure, thereby augmenting the work of the heart, but through accelerating the rate also shorten diastole, which is the rest period of the heart and the time during which coronary filling is probably maximal The relation of exercise to cardiac pain has been studied quantitatively by Wayne and Laplace. They subjected 11 individuals who suffered from cardiac pain on exertion to an exercise tolerance test by means of stair-climbing. Wayne and Laplace found that in each individual the amount of exercise required to produce pain was approximately constant. They further showed that in these cases the appearance and disappearance of the pain is much more closely related to the heart rate than to the arterial pressure, an observation which indicates the enormous importance of the rest period in the presence of decreased coronary flow.

(*b*) Cardiac pain is especially apt to follow a heavy meal. Gladstone[11] has shown that during digestion cardiac output is increased an average of 25 per cent; since the mean arterial pressure tends to rise a little, there is even more than a corresponding increment in cardiac work. That this increase in the work of the heart is correlated with the frequency of post-prandial pain is indicated by the work of Wayne and Graybiel. They found in 6 subjects with angina of effort that after a heavy meal the amount of exercise required to produce pain was decreased by 25 per cent. On the other hand, they found that inflation of the stomach with air, even when sufficient to displace the heart and produce epigastric discomfort, had no effect on the exercise tolerance. However, there may also be cases in which gastric distention, presumably through some reflex influence, is significant in the production of pain, for Wayne and Graybiel describe an individual in whom anginal attacks sometimes came on without relation to exercise and in whom inflation of the stomach with air did produce cardiac pain. Light may be hrown on the mechanism by which gastric distention favors cardiac pain by the experiments of Gilbert, LeRoy and Fenn.[10a] They find that inflation of a balloon within a dog's stomach caused reduction in blood flow through the left coronary artery in 11 of 13 observations. Gilbert and his associates attribute the decrease in coronary flow to reflex vasoconstriction initiated by the gastric distention.

(*c*) Rothschild and Kissin[37] showed that if patients subject to cardiac pain breathe an oxygen-poor atmosphere, the pain may be induced. The increase in cardiac output that results from anox-

emia is presumably responsible, although the low oxygen saturation of the coronary blood may also be concerned in producing the metabolic changes in the myocardium responsible for the pain. In support of the latter conception is Kissin's[22] demonstration that pain develops in an exercising skeletal muscle more readily when there is anoxemia, even when blood flow is not retarded.

(*d*) In anemia the work of the heart is increased (page 576); cardiac pain may occur and disappear when the hemoglobin rises. Here, again, the low oxygen saturation of the arterial blood may also affect myocardial metabolism directly.

(*e*) In insulin hypoglycemia cardiac output is increased That individuals with coronary sclerosis are liable to cardiac pain during hypoglycemia is well known (page 584).

(*f*) Epinephrin increases the work of the heart through augmenting both cardiac work and mean arterial pressure Levine, Ernstene and Jacobson[25] produced cardiac pain in 10 of 11 patients with coronary artery disease by the injection of epinephrin The pain was doubtless due to the increase in cardiac work and acceleration of the rate, for there is good evidence that epinephrin dilates the coronary arteries in man.

(*g*) When thyroid extract is administered to elderly patients with myxedema (and doubtless often coronary arteriosclerosis), anginal pain often develops and forces diminution in dosage (see page 595) Here the augmentation in the work of the heart due to the rise in metabolic rate and acceleration of the heart rate are presumably responsible for the pain

6 The relief of cardiac pain by nitrites is in excellent harmony with the theory that the pain is due to ischemia of the myocardium. Voegtlin and Macht[47] and others have shown that nitrites increase coronary flow. Smith[40] found that, through dilatation of collaterals, nitrites may improve the circulation in the infarcted area of the myocardium resulting from ligature of a coronary branch Wayne and Laplace have found evidence that the action of nitrites in dilating the coronary vessels is more important than the lowering of blood pressure in the relief of anginal pain; they may afford relief at a time when the blood pressure is little changed.

The lines of evidence just sketched establish that ischemia of the myocardium can produce cardiac pain, and indicate strongly that this mechanism mediates at least most forms of cardiac pain *other than those of psychoneurotic origin How myocardial* ischemia produces cardiac pain is not entirely known. However, some light has been thrown on the matter by recent studies of Lewis, Pickering and Rothschild[27] on the development of pain during exercise of skeletal muscle when the circulation is obstructed. It has long been thought (Burns,[6] Potain[35]) that cardiac pain is analogous to the pain—intermittent claudication—that develops

during walking in the muscles of the lower extremities of individuals with arteriosclerotic, thromboangiitic, or other narrowing of the arteries In both cases the pain is precipitated by exercise and relieved by rest; further, as pointed out by Lewis, both varieties of pain are continuous and not throbbing and have other characteristics in common. Lewis, Pickering and Rothschild found that if an extremity with the arteries constricted is exercised until pain develops, release of the constriction is followed by relief of the pain within a few seconds even though the exercise is continued. On the other hand, if the constriction is maintained but the exercise stopped, the pain continues until blood is permitted to flow again. Lewis and his associates interpreted these observations as indicating that the pain is due to stimulation of the nerve endings by a substance—of as yet unknown nature, which they term "factor P"—produced as a result of the contraction of the muscle cells. With intact circulation, this substance is removed before it reaches a concentration sufficient to produce pain But when coronary flow is diminished the substance may accumulate in concentration above the threshold for the production of pain. Presumably, this will occur the more readily the greater the work of the heart; Lewis, Pickering and Rothschild found in experiments on the constricted arm that the rapidity with which pain develops varies directly with the amount of work performed, whether the latter is altered by changing the rate or the vigor of contraction. Apart from a few details, the work of Lewis *et al.* has been confirmed by Katz, Lindner and Landt.[20] Apparently oxygen deficiency favors the accumulation of the pain-producing substance, for Kissin found that pain comes on more quickly when the subject exercises while breathing an atmosphere poor in oxygen In accord with these findings, Riseman and Brown[36] found that 11 of 17 patients with angina pectoris could do more work before developing pain while breathing high concentrations of oxygen.

It would thus appear that, as so ably maintained by Keefer and Resnik,[21] *myocardial ischemia produces anginal pain through the intermediacy of myocardial anoxemia;* angina pectoris is the cry of the heart for more oxygen.

Pathogenesis of Myocardial Ischemia.—The immediate cause of the myocardial ischemia which is evinced by cardiac pain is almost always decrease in blood flow through one or more coronary branches In the classical forms of angina pectoris as described by Heberden this is due to arteriosclerotic or thrombotic narrowing or occlusion along the coronary trunks. In syphilitic aortitis it is the result of stricture of the coronary orifices Rare causes of coronary obstruction are embolism and blocking of a coronary mouth by aortic vegetations in bacterial endocarditis. In aortic regurgitation it appears that the alterations in the dynamics of the

circulation resulting in low diastolic pressure diminish coronary flow and thus predispose to myocardial ischemia (page 475). The same is true in the far rarer arteriovenous aneurysm (page 579). It is also probable that the small cardiac output in aortic stenosis decreases coronary flow and thus results in the not uncommon anginal attacks; however, the patients are mostly elderly and the situation complicated by coronary arteriosclerosis and sometimes by calcareous lesions of the root of the aorta narrowing the coronary orifices.

The pathogenesis of myocardial ischemia should not, however, be considered solely from the point of view of the absolute volume of coronary flow; variation in the volume of blood flow required by the myocardium is also significant It seems obvious that the greatly hypertrophied left ventricle of hypertension or aortic valvular defect requires a much augmented volume of blood flow, not only because of the greater muscle mass but also because of the increased amount of work it is performing. Under such conditions a smaller degree of coronary narrowing suffices to produce deficient blood flow than if the myocardium were of normal thickness and performing a normal amount of work Actually, in patients with hypertension and an enormous left ventricle there may be anginal attacks over a long period and yet at necropsy only moderate coronary arteriosclerosis is found. It has been my experience that anginal pain in individuals with little cardiac enlargement is more apt to be followed by coronary thrombosis than in those with very large hearts (usually due to hypertension). This is probably correlated with the greater coronary narrowing required to produce pain when the heart is not much enlarged.

The question arises: Since, of course, the coronary narrowing is always present, why is the myocardial ischemia and consequent pain paroxysmal? In the large majority of cases, in which the pain is precipitated by exertion or excitement and relieved by rest, the answer seems evident The exertion or excitement increases the work and consequently the volume of blood flow required by the heart. That the work of the heart is actually increased in angina pectoris has been demonstrated by Starr[42] and his collaborators, who found in 4 cases that the work of the left ventricle was greater during the pain than when comfortable. At the same time the rate is accelerated, which has the twofold effect of shortening the recovery period of the heart and also abbreviating the "total diastole" per minute, which appears to be the part of the cardiac cycle in which most of the filling of the coronary vessels occurs Moreover, there is every reason to believe that in health the greater coronary blood flow necessitated by exercise is largely mediated through coronary dilatation; with sclerosis and calcification of the coronary arteries, this adjustment may be greatly hampered. As

explained above (page 416), a similar mechanism doubtless accounts for the precipitation of cardiac pain by a hearty meal. Why some anginal attacks occur at rest, even during sleep (angina of decubitus), is not known. This is especially apt to occur in aortic regurgitation. Some patients with arteriosclerotic heart disease have paroxysms of either or both cardiac asthma and pain at night. Presumably factors akin to those producing the dyspnea are concerned in the genesis of the pain; however, the entire subject is obscure (page 151). It has often been suggested (*cf.* Gilbert[10]) that coronary constriction or failure of coronary dilatation called for by the needs of the heart muscle, of nervous or humoral origin, may be concerned in the genesis of many anginal paroxysms. Since the caliber of the coronaries is known to be regulated by neural and humoral mechanisms, such a conception seems plausible. But as yet it has little factual support.

Nervous Pathways of Cardiac Pain.*—The pain is apparently transmitted from the sensory endings in the heart by nerve fibers which run in the adventitia of the coronary arteries, for Sutton and Lueth and Katz and his associates found that interruption of this pathway by painting with alcohol or other means abolished the pain produced by tightening a loop around the vessel. According to the description given by White,[51] the sensory impulses then travel along sympathetic fibers to enter the superior middle and inferior cervical ganglia, as well as directly across the posterior mediastinum into the upper thoracic sympathetic ganglia. From the sympathetic chain the impulses enter the spinal cord *via* the white rami communicantes and posterior roots of the upper five thoracic segments. White states that the direct sensory communications between the cervical sympathetic ganglia and the spinal cord which have been described are of no clinical importance. Apparently the vagus does not contain afferent fibers leading to pain, the impulses from the heart, as from other viscera, which produce pain travel only in the sympathetic nerves. Knowledge of these pathways of cardiac pain is of great significance for the relief of cardiac pain by injection (page 774).

Relations of Cardiac Pain to Heart Failure.—Everyday clinical observation shows that there is no direct, if any, correlation between cardiac pain and heart failure. Some of the most severe forms of heart failure, for example in mitral disease, run their entire course without any pain. It is not always that the patient is insensitive to pain, for the latter may be severe as a result of engorgement of the liver On the other hand, severe cardiac pain commonly results from coronary arteriosclerosis in the absence of cardiac failure as

* The recent monograph of Miller[31] contains a detailed description, with a highly instructive series of diagrams, of the nervous pathways concerned in the transmission and reference of cardiac pain

manifested by engorgement of the pulmonary circuit or systemic veins; Heberden emphasized that dyspnea is not a feature of angina pectoris. It is true that heart failure may result from coronary thrombosis, but pain and cardiac insufficiency are obviously merely the results of a common cause.

To a certain extent, indeed, there is an antagonism between cardiac pain and insufficiency of the right side of the heart. It is a common experience in arteriosclerotic heart disease that anginal pain becomes less marked or disappears with the advent of right heart failure and systemic venous engorgement. This may occur with dramatic suddenness when the cardiac insufficiency is precipitated by the onset of auricular fibrillation Mackenzie and others have attributed this phenomenon to dyspnea, forcing the patient to cease exertion before it reaches the level at which pain is evoked. However, I have repeatedly observed the disappearance of anginal pain, which previously occurred even at rest, when the right side of the heart failed with swelling of the systemic veins and liver and the appearance of edema. In such cases the following mechanism may be concerned. Ischemia due to coronary arteriosclerosis affects predominantly the left ventricle, the thinner-walled right ventricle is much less affected, and infarcts confined to the right ventricle are great rarities. With the onset of right heart failure, the output of the right ventricle is decreased and with it the work of the left ventricle, so that the latter chamber can get along with a smaller volume of blood flow.

Another factor that may militate against the development of cardiac pain in right heart failure is suggested by the finding of Gross and Blum[15] in the dog that the collateral circulation opened up after ligating a coronary artery is markedly augmented by previous ligation of the coronary sinus. Similarly, Ungerleider, Kerkhof and Fahr[45] observed that raising the pressure in the coronary veins tends to prevent infarction after coronary artery ligation. On the other hand, Gregg and Dewald[14] found that acute obstruction of coronary veins does not prevent failure of contraction in a myocardial area whose artery has been ligated. The problem of whether or not raising coronary venous pressure facilitates the development of collateral circulation in an ischemic area deserves further investigation

It is a common experience that cardiac pain ceases after a major coronary thrombosis even though the patient recovers well enough to be up and about and the blood pressure returns close to its previous level. In such cases it is to be presumed that the pain was due to ischemia of the portion of the heart muscle supplied by the vessel that was subsequently occluded The necrosis of the myocardial mass in question, including the nerves, removes the source of the pain.

In brief, cardiac pain is not a symptom of heart failure, although both pain and failure may result from a common cause.

Other Forms of Cardiac Pain.—It has been seen that there is excellent evidence that the common forms of cardiac pain (angina pectoris) are evoked by ischemia of the myocardium. The question next arises whether there are also other forms of cardiac pain.

There is no reason to believe that lesions of the *endocardium* produce pain. Uncomplicated endocarditis, even when ulcerative, is painless.

The *myocardium* appears to be insensitive to stimuli other than those resulting from decrease in blood flow and perhaps also anoxemia. Sutton and Lueth were unable to evoke pain responses in the dog by piercing various portions of the myocardium with a needle, tearing through the myocardium by means of sutures, or injecting 10 per cent ammonium hydroxide or 80 per cent alcohol into the myocardium Nor did pinching of the myocardium of a monkey with forceps produce a pain response. These findings are in harmony with the common clinical experience that affections of the myocardium other than those due to diminished blood flow do not result in pain.

The *pericardium* presents a more complicated problem. Most often, pericarditis, whether dry or with effusion, does not result in pain However, there are exceptional cases in which inflammation of the pericardium is accompanied by pain. The pain may be dull or lancinating, or merely a feeling of tightness; it may be localized in the precordial region, referred to the left side of the neck, the upper abdomen or the back, or radiate to the left shoulder like that of coronary artery disease Capps[6] studied the sensitivity to pain of the pericardium in individuals with pericardial effusion by puncturing the parietal pericardium with a trocar and then scratching the serous surfaces by means of a wire passed through the trocar. He found that both the visceral and parietal surfaces of the pericardium are insensitive to scratching—good evidence that when pain does occur in pericarditis it is not due to the rubbing of the roughened surfaces on one another Similarly, Sutton and Lueth found that stretching and tearing the visceral pericardium in dogs produced no pain response. The only way in which Capps was able *to elicit pain from the human pericardium* was by puncture of the parietal pericardium at the level of the fifth and sixth left interspaces lateral to the mammary line, which caused pain in the left side of the neck along the trapezius ridge. Puncture of the parietal pericardium at higher levels caused no pain. From these and other observations Capps believes that the phrenic nerve supplies at least the lower portion of the fibrous pericardium with nerves that carry painful stimuli. Capps concludes that when pericardial *disease is* associated with pain, the latter results in one of three ways: (1) A large effusion may cause a dull ache or feeling of

oppression through stretching of the parietal pericardium (protopathic pain), although in my experience most large effusions have been painless. (2) Through accompanying pleuropericarditis and mediastinitis. This is probably the usual cause of pain in rheumatic pericarditis. (3) When the pericarditis results from myocardial infarction due to coronary thrombosis, the myocardial lesion produces pain. That the pericarditis over a myocardial infarct, *per se*, is responsible for pain remains to be demonstrated

The *aorta* has played a great rôle in connection with theories of angina pectoris. Supported by the great authority of Allbutt[1] and Wenckebach,[50] the theory long enjoyed considerable vogue that the common forms of cardiac pain are due to distention* by the arterial pressure of a diseased aorta with consequent stimulation of nerve endings located especially in the adventitia. The fact that anginal pain is precipitated by exertion was explained by the rise in aortic pressure and consequent distention of the root of the aorta. The theory really had little support other than the fact that lesions of the aorta—either arteriosclerotic or due to syphilitic or other forms of aortitis—are present in most patients with cardiac pain. The aortic theory has been largely abandoned since the clinical picture of coronary thrombosis has become generally known and with it the other evidence, summarized above, showing that myocardial ischemia produces pain. Moreover, recent experiments by Sutton and Lueth have shown that in the dog mechanical distention of the aortic arch, ascending aorta and aortic ring does not produce pain, although it may result in paroxysmal dyspnea. These experiments would seem to controvert the view that exertional angina is due to the distention of the aorta by the blood pressure However, it seems probable, though more evidence is needed on this point, that in syphilitic aortitis inflammation of the connective tissue around the aorta (periaortitis) and pressure by the dilated aorta on surrounding structures may produce the continuous pain or feeling of oppression under the upper sternum from which these patients sometimes suffer. Whether a similar pain can result from arteriosclerotic dilatation of the aorta remains to be ascertained

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CHAPTER XXIV

FAILURE OF THE LEFT SIDE OF THE HEART. I. THE GENERAL PICTURE

THE most common forms of circulatory failure encountered in the office of the general practitioner are those in which the onset is with failure of the left side of the heart Either the left ventricle or the left auricle may be the chamber meeting the initial strain, in both cases the disturbance in circulatory dynamics is fundamentally the same. Initial left auricular failure results from mitral stenosis Failure of the left ventricle results from diseases in which the work of this chamber is increased, its circulation impaired, or its muscle diseased Apart from the terminal peripheral circulatory collapse which closes most of our lives, left ventricular insufficiency is the most common form of circulatory failure, for it includes essential and nephritic hypertension, arteriosclerotic and syphilitic disease of the coronary arteries to the left ventricle, defects of the aortic valve, and mitral disease with predominant regurgitation In each of these conditions, the initial stage of circulatory failure is most often that of isolated insufficiency of the left side of the heart, which may last in uncomplicated cases for years, even to the fatal termination, or be joined after a longer or shorter interval by the consequences of failure of the right heart We shall discuss individually each of the conditions in which circulatory failure is initiated by insufficiency of the left side of the heart. But before so doing, it may be useful to outline the clinical features common to all varieties of left-sided heart failure.

THE SYNDROME OF FAILURE OF THE LEFT SIDE OF THE HEART

The clinical picture of uncomplicated failure of the left side of the heart consists in symptoms and signs resulting from engorgement of the pulmonary circuit and diminished output of the left ventricle. These positive characteristics contrast with the absence of systemic venous congestion, which evinces the functional integrity of the right side of the heart. The symptomatology is completed by the local signs of dilatation of the left ventricle.

Of the two consequences of left-sided failure, pulmonary engorgement predominates in chronic cases, while the consequences of diminished output of the left ventricle stand in the foreground when

this chamber gives way suddenly. The result is two main variants of the syndrome of left-sided failure:

1. *Chronic Left-sided Failure.*—When failure of the left heart is of gradual onset or considerable duration, the symptomatology is predominantly that of pulmonary engorgement, namely, dyspnea, orthopnea, cyanosis, cough, hemoptysis, etc. In sharp contrast, the consequences of decreased output of the left ventricle—fall in arterial pressure, pallor, syncope and other symptoms of cerebral ischemia—are absent or appear only paroxysmally. In other words, the picture is what Harrison[1] termed backward failure into the lungs and not his forward failure (page 29).

2. *Acute Left-sided Failure.*—With sudden failure of the left heart, the clinical manifestations are most often preponderantly those of decreased output of the left ventricle. The arterial pressure falls, the skin is pallid and sweating, and there may be syncope, vertigo or other consequences of decreased cerebral blood flow. Here, forward failure predominates over backward failure; we are faced by the dramatic picture of *cardiac shock* (page 653). The commonest cause of this acute form of left-sided failure is coronary thrombosis

The rationale of this dissociation of the two aspects of failure of the left heart—forward failure predominating in the acute cases, backward in the chronic—is probably the following: When the failure evolves gradually, there is time for the development of compensatory mechanisms involving increase in the circulating blood volume (page 71). This increase in blood volume unfortunately tends to accentuate the pulmonary engorgement, but the latter in turn so augments the filling of the left ventricle that, in accord with Starling's law, the functionally impaired chamber maintains the cardiac output at but little under its previous level. On the other hand, when the left ventricle fails suddenly, as in coronary thrombosis, the compensatory increase in blood volume is not developed at first with the twofold result that the cardiac output falls and most often the pulmonary engorgement is not as pronounced as in the chronic cases.

Pulmonary Engorgement in Left-sided Failure.—The picture of pulmonary engorgement has been described in detail in Chapter XIII Briefly it consists in:

Exertional dyspnea, the symptom par excellence of left heart failure, most often the first manifestation, and the one which persists most obstinately. In a general way, it may be said that in left-sided heart failure, dyspnea dominates the symptomatology more than in other forms of circulatory failure.

Paroxysmal dyspnea, or cardiac asthma, while not invariably present, is a very characteristic manifestation of left ventricular failure, being far more common than when the lungs are engorged

as a result of the left auricular failure of mitral stenosis. Nocturnal paroxysms of dyspnea are not rarely the first symptom of left ventricular failure in a patient who is not aware of exertional dyspnea during the day

Orthopnea occurs with relatively low grades of dyspnea in left-sided heart failure Orthopnea is much more prominent in the dyspnea of pulmonary engorgement than in that of primary right heart failure, of peripheral circulatory failure, or of acidosis, in all of which it is most characteristically absent despite marked tachypnea and obvious air hunger

Cough may also result from the pulmonary engorgement of left heart failure In cough of obscure origin in the elderly, the possibility of underlying coronary sclerosis with left ventricular failure is always to be borne in mind The cough is often dry, but in other cases it is productive of *expectoration*, the characteristics of which have already been described (page 214) Blood-streaked sputum is common. Copious *hemoptysis* is rare but does occur, especially in mitral stenosis *Wheezing*, like in bronchial asthma, may be a complaint.

Hoarseness is a rare symptom produced by compression of the left recurrent laryngeal nerve by the engorged left pulmonary artery (page 507).

Cyanosis is often present and may be severe, but is not rarely absent despite severe left-sided failure. In a general way, and with many exceptions, it may be said that dyspnea predominates over cyanosis in left-sided failure and cyanosis over dyspnea in insufficiency of the right side of the heart. Cyanosis is apt to be especially pronounced in long-standing left heart failure with brown induration of the lungs When pulmonary edema develops, cyanosis often becomes intense

Physical examination of the lungs may be negative despite severe left heart failure. Often, however, "functional emphysema" results from the engorgement of the pulmonary vessels, which interferes with the expiratory collapse of the lungs and thus tends to maintain the lungs in an average position closer to that of inspiration than in health. With improvement in the accomplishment of the left side of the heart, the distention of the lungs recedes, while it becomes more pronounced during acute exacerbations of left-sided failure. At least 63 per cent of Weiss and Robb's[3] patients with severe cardiac asthma due to left ventricular failure presented the increased anterio-posterior diameter of the chest and other physical signs characteristic of pulmonary emphysema The frequency with which left-sided failure in elderly and arteriosclerotic subjects results in emphysematous distention of the thorax deserves emphasis; it has seemed to me that often when the diagnosis of coincident but independent pulmonary emphysema and hypertension with arterio-

sclerotic heart disease is made, the former is merely a consequence of the latter. Moist râles at the bases of the lungs are a frequent finding in left-sided failure, but may be absent even when the latter is severe.

As might be expected from the engorgement of the pulmonary vessels, the *vital capacity* is decreased. Likewise, Weiss and Robb found the total volume of the pulmonary air space decreased and the residual air increased.

The engorgement of the pulmonary circuit is also revealed by the roentgen findings (page 218).

In the large majority of instances of left-sided failure, tests with saccharin or other substances (page 55) reveal that *blood flow* through the lungs is markedly slowed; saccharin times of over forty seconds are common. Only in rare instances does the arm-to-tongue circulation time approach the normal, evidently because the right ventricle increases its work sufficiently to compensate for the weakness of the left side of the heart (page 210). It may be repeated that measurement of the arm-to-tongue circulation time is one of the most useful tests for left-sided failure. Especially characteristic of the early stages of left heart failure is prolonged arm-to-tongue (saccharin) time with normal arm-to-lung (ether) time (page 210).

Edema and *infarction* of the lungs and *bronchopneumonia* are such common complications of left heart failure that they are to be regarded as part of the clinical picture.

Manifestations of Diminished Cardiac Output in Left-sided Heart Failure.—When the left ventricle fails suddenly, as in coronary thrombosis, the outstanding symptoms are most often those of decreased cardiac output. The patient is pale or exhibits a pallid cyanosis, the skin is covered with cold sweat, dyspnea or orthopnea are most often not pronounced, the extremities are cold, the peripheral veins are collapsed, and the arterial pressure has fallen. Weakness is often the main complaint. Vomiting is common. Vertigo or syncope due to inadequate cerebral blood flow are the rule. Oliguria is pronounced The symptomatology is thus practically identical with that of traumatic shock or other forms of shock due to peripheral circulatory failure Only in this case the decrease in cardiac output which causes the symptoms is of primarily cardiac and not of peripheral origin, for which reason the clinical picture is appropriately termed *cardiac shock*. To avoid repetition, details of the clinical manifestations of cardiac shock will be postponed to the section on coronary thrombosis (page 451).

Cardiac Manifestations of Left-sided Failure.—These vary with the nature of the underlying condition and are described in the following sections. It may be mentioned here, however, that accentuation of the second pulmonic sound is a common manifes-

tation of all varieties of left-sided heart failure, and not at all characteristic of mitral disease. It should also be borne in mind that through the intermediacy of hypertension of the lesser circulation, left ventricular failure produces enlargement of the pulmonary conus of the right ventricle with consequent "mitralization" of the heart. I have repeatedly known patients with left ventricular failure to be considered as suffering from mitral stenosis because of the presence of gallop rhythm (mistaken for a presystolic murmur), accentuation of the pulmonic second sound, and "mitralization" in the roentgenogram Parenthetically, it may be mentioned that while left ventricular failure may produce prominence of the pulmonary conus on dorso-ventral illumination, it does not result in the marked bulging of the left auricle into the retrocardiac space which is present in many cases of mitral stenosis To be sure, there is some dilatation of the left auricle in left ventricular failure, but it does not compare in magnitude with that often present in mitral stenosis.

The Systemic Veins in Left-sided Heart Failure.—Engorgement of the systemic veins and consequent swelling of the liver and peripheral edema are absent in isolated left-sided failure. Measurement of the pressure within an antecubital vein reveals it to be below or close to the upper limit of normal. This is true in even very severe left heart failure. Thus, in a patient with acute pulmonary edema due to left ventricular failure, Hitzig, King and the writer[2] found the venous pressure to be but 6 cm. in the presence of arm-to-tongue circulation time of twenty-eight seconds (saccharin method), we have made many similar observations. It is only when the right ventricle also gives way that any considerable elevation of venous pressure develops. However, occasionally one encounters relatively slight elevation of venous pressure, to about 10 cm., in patients with an otherwise typical clinical picture of left ventricular failure. It seems probable, though not proved, that one or more of three mechanisms may be concerned in producing this slight venous hypertension:

1. The right ventricle performs increased work because of the elevation in pressure in the pulmonary circuit due to left heart failure. The right ventricle can overcome this increased resistance only by means of greater diastolic filling and higher diastolic intraventricular pressure, the latter of which is reflected in the venous pressure. It is therefore probable that slight elevation of venous pressure in the presence of left heart failure does not in itself connote considerable functional impairment of the right ventricle, but is simply a manifestation of the mechanism by which the right ventricle accommodates itself to the increased work necessitated by the pulmonary hypertension.

2. When the left ventricle is greatly hypertrophied and dilated it

is possible that the interventricular septum may bulge into the right ventricle sufficiently to impede the filling of the chamber and thereby elevate the venous pressure (page 447).

3. The pulmonary engorgement due to left-sided failure diminishes the elasticity of the lung. This in turn elevates intrapleural pressure. It has been seen that increased intrapleural pressure entails augmentation of peripheral venous pressure (page 104). To a certain extent, then, a similar mechanism operates to produce slight elevation of venous pressure in left-sided failure as in emphysema and in pulmonary engorgement.

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CHAPTER XXV

FAILURE OF THE LEFT SIDE OF THE HEART: II. HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE

Among adults, by far the commonest form of cardiac insufficiency is left ventricular failure due to hypertension and/or coronary arteriosclerosis These two conditions are so often associated that they will be considered in the same chapter In the vast majority of hypertensive patients, heart failure does not appear until after the development of a high degree of coronary arteriosclerosis, in the causation of which the hypertension plays a part It thus appears that most instances of heart failure in hypertension are the result of both the increased work of the heart due to the high blood pressure and the decreased functional capacity of the myocardium which is an inevitable consequence of diminished blood supply. Contrariwise, arteriosclerosis alone often produces heart failure without hypertension having been present at any time. In a necropsy study of 928 cases of arteriosclerotic heart disease, Clawson[14] found that hypertension had been present in 69 per cent

ESSENTIAL HYPERTENSION

Individuals with high blood pressure may be afflicted with cardiac symptoms of two varieties, namely, those of heart failure and angina pectoris. Either may usher in the clinical course of essential hypertension, and a cardiac death is the most common termination of the disease; 254 of Bell and Clawson's[6] 420 fatal cases of essential hypertension succumbed to cardiac manifestations The enormous importance of high blood pressure in the causation of cardiac disease is indicated by White and Jones[64] finding that in New England hypertension is concerned in about 30 per cent of all cases of heart disease Many patients with essential hypertension are "cardiacs" from beginning to end. They may suffer from angina pectoris or heart failure for years, or the first manifestation of the disease may be fatal coronary thrombosis, the underlying hypertension being first revealed at necropsy by left ventricular hypertrophy and renal arteriolosclerosis.

On the other hand, cardiac symptoms may be absent or in the background Numerous persons with very high blood pressure are able to perform hard physical work for years without undue shortness of breath. Heart failure is unusual in those forms or stages of essential hypertension—especially common in women—in which the blood pressure exhibits wide fluctuations within a few hours and

where the picture is dominated by such symptoms as vertigo, psychomotor unrest, hot flushes, and transient headache; palpitation is common in these individuals, but does not indicate imminence of heart failure or angina. If the patient's activities are curtailed as a result of a cerebral vascular accident or the consequences of renal insufficiency, subjective symptoms of circulatory failure are *often absent or minimal even though there are such objective signs* of left ventricular insufficiency as dilatation, gallop rhythm, and prolongation of the pulmonary circulation time.

In the history of most patients with essential hypertension who develop heart failure, one can discern three stages:

1. The stage of cardiac compensation.
2. The stage of isolated left ventricular failure.
3. The stage of combined left- and right-sided failure.

Of course, this typical "natural history" of the circulation in essential hypertension may be interrupted in any stage by coronary thrombosis, cerebral hemorrhage, renal insufficiency, or other intercurrent complications.

The Stage of Cardiac Compensation.—In the resting individual, the work of the left ventricle is expressed with an error of the order of only 1 per cent by the product of the average arterial pressure and the cardiac output (Starling[10]). Since the cardiac output is little changed in compensated hypertension, it is evident that the work of the left ventricle is increased in direct proportion to the rise in the average arterial pressure.

The increase in the work of the left ventricle results in hypertrophy of the chamber. The considerations discussed in Chapter XVIII indicate that initially the left ventricle performs the increased work by a mechanism involving dilatation, but this is replaced by hypertrophy while still of so slight a grade as not to be demonstrable. In cases of essential hypertension without heart failure, notably those which succumb to cerebral hemorrhage or an intercurrent complication, one often finds thickening of the wall of the left ventricle without enlargement of its cavity. Indeed, the latter may appear unusually small, the so-called concentric hypertrophy, but we have seen (page 311) that this is probably an artefact due to postmortem contraction and the cavity was not actually diminished in size during life. In many instances of arterial hypertension, the development of such faultless compensation by hypertrophy with almost no dilatation is doubtless facilitated by the gradual evolution of the elevation in blood pressure, and the fact that the *latter is usually intermittent in its first stages. In other* cases of hypertension succumbing to cerebral hemorrhage or other noncardiac causes, and in which there was no history of cardiac symptoms, the hypertrophy of the left ventricle may be found to be accompanied by well-marked dilatation of the chamber. However,

examination of the lungs in such cases usually reveals evidence of chronic passive congestion, so that despite absence of subjective symptoms a considerable degree of left-sided failure was present.

The hypertrophy of the left ventricle may so increase the strength of its systole that it empties as completely as in health despite the increased resistance in the aorta. Complete emptying may also be aided by the relatively longer duration of systole in hypertension than in health (Schlomka and Theiss[59]). If this is the case, the functional capacity of the circulation may be practically as great as in health, and the individual capable of hard work without untoward dyspnea Careful examination may reveal no abnormalities other than the high pressure in the systemic arteries and the hypertrophy of the left ventricle. In more detail, the findings in such a well-compensated case of essential hypertension are as follows:

Physical Findings.—The apex beat is within the mid-clavicular line, most often at its usual height, exceptionally displaced downward an interspace Often, especially when the patient leans to the left, the heaving, forceful character of the apex beat is evident. Such a heaving apex beat, when present, is pathognomonic of left ventricular hypertrophy, but is not to be confused with the diffuse and feeble, even though prominent, impulse of a dilated or overacting heart. It should be remembered that the apex beat may not be palpable, despite marked cardiac hypertrophy, especially if there is emphysema (H. A. Derow). The closure of the aortic valve may result in a palpable impulse in the second right interspace, notably when diastolic hypertension is accompanied by elongation and sclerosis of the aorta. In such cases, powerful expansile pulsation is often to be felt in the manubrial notch. The elongation of the aorta in hypertensive patients may also result in prominent pulsation and tortuosity of the carotid artery in the right side of the neck.

Percussion reveals that the heart is not notably enlarged to either the left or the right. The increased mass and firmness of the heart may be evident to the percussing finger. Exceptionally, it is possible to demonstrate by percussion downward elongation of the left ventricle. Increase in retromanubrial dulness may result from dilatation and elongation of the aorta with consequent wider approximation of the vessel to the anterior chest wall

On auscultation, the rhythm is regular. The rate is most often normal, occasionally somewhat slow. However, in those cases of essential hypertension with a clinical picture simulating Graves' disease, the heart is accelerated without any connotation of heart failure. The first sound at the apex may be booming and seem prolonged, but there is no gallop rhythm. The second apical sound is generally loud. Accentuation of the second sound at the aortic area has long been regarded as the characteristic auscultatory find-

ing in high blood pressure, but Janeway[32] failed to detect it in 105 of 389 patients with arterial hypertension, and the accentuation was but slight in 78 of the others. Absence of accentuation of the aortic second sound may be due to emphysema or obesity, or the cause may not be obvious Often, the aortic second sound is reduplicated and may be ringing in quality (*bruit de tabourka*). The ringing quality is not due to the hypertension but to associated sclerosis and calcification of the aorta and aortic cusps. It should be remembered that the aortic second sound may be greatly accentuated and ringing in the absence of hypertension as a result of arteriosclerosis with consequent elongation of the aorta, which is thus more closely approximated to the chest wall. Systolic murmurs are often audible at the apex and base; in well-compensated patients without cardiac dilatation or old endocarditic defects, they may be due to atherosclerotic changes in the valves and aorta or, in the case of the apical murmurs, of cardiorespiratory origin. Diastolic murmurs are far less common and are probably most often due to atherosclerotic changes.

Roentgen Findings.—Fluoroscopically, no abnormality of the size or shape of the cardiac silhouette may be evident, even though the blood pressure has been elevated for years. More often, rounding of the lower segment of the left border and downward elongation of the left ventricle into the shadow of the diaphragm without definite increase in the transverse diameter of the heart testify to the existence of hypertrophy without notable dilatation of the left ventricle (page 353). However, there are also patients with essential hypertension in whom dilatation of the left ventricle is indicated by moderate enlargement to the left and yet there are no subjective symptoms of heart failure; presumably, such individuals are close to the border of clinical decompensation, and yet I have seen cases in which this did not appear for years. The increased density of the left ventricle may be discernible. Most, but not all, patients with high blood pressure of considerable standing exhibit elongation and dilatation of the aorta

Electrocardiographic Findings.—In view of the hypertrophy of the left ventricle, one would anticipate rotation of the electrical axis of the heart to the left. But the electrocardiogram does not always show this In 50 hypertensive patients, O'Hare and Walker[50] found left axis deviation in 30, a normal electrical axis in 19, and questionable right axis deviation in 1. Master[45] observed left axis deviation in 74 per cent of 152 individuals with high blood pressure It has seemed to me that in faultlessly compensated cases of essential hypertension with no evident dilatation, the incidence of left axis deviation is even less. The left axis deviation is often accompanied by abnormally high voltage of the *Q-R-S* complex. But if the myocardium is damaged as a result of coronary artery disease, the

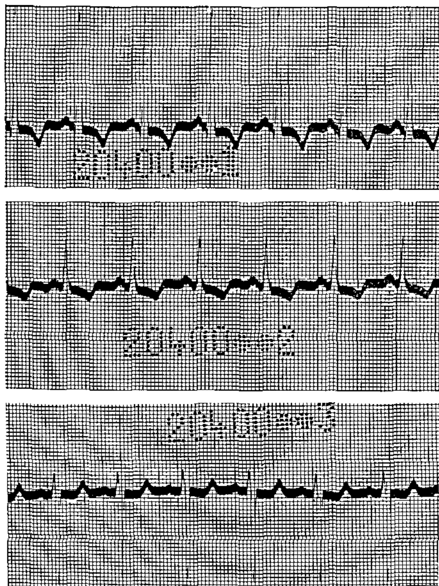


Fig 17 —Electrocardiogram of a patient with great hypertrophy and dilatation of the left ventricle The voltage of the *Q-R-S* complex is high, rotation of the electrical axis to the left is revealed by the upward direction of the major deflection of this complex in the first lead and the downward direction in the third lead The inversion of the *T* wave in the first and second leads is common in great left ventricular enlargement and may indicate deficient blood supply to this chamber

voltage of the *Q-R-S* complex may be low despite very high blood pressure. The combination of marked left axis deviation and high voltage of the *Q-R-S* complex is especially common in severe hypertension in relatively young individuals.

As shown by Master[11] and Barnes and Whitten,[5] the left axis deviation is often, but by no means always, accompanied by inversion of the *T* wave in the first lead. The most characteristic picture, when present, is the following: high voltage of the *Q-R-S* complex in the first lead followed by an inverted *T* wave, the anacrotic limb of which is convex upward and usually "takes off" from the *R-S* deflection below the isoelectric level. The *T* wave may also be inverted in the second and precordial leads. Complementary to the depression of the *S-T* interval in the first lead may be an elevation of this interval in the third lead. In many of the cases with this electrocardiographic picture, postmortem observation shows that pronounced coronary narrowing is absent. Furthermore, precisely the same electrocardiographic findings are encountered in aortic valvular disease in young subjects. These observations indicate that the electrocardiographic picture described is indicative of marked hypertrophy of the left ventricle. This view is supported by the fact that the same electrocardiogram in the third lead may be encountered in the right ventricular hypertrophy of pulmonic stenosis or pulmonary vascular disease. In the patients with hypertension or aortic disease in whom I have encountered the combination of high voltage and inverted *T* wave in the first lead, the hypertrophy was accompanied by considerable dilatation of the left ventricle, and most often some subjective or objective evidences of left ventricle failure were present. Perhaps the most probable explanation of the electrocardiographic picture in question, though one which is not proved, is that it is due to relative ischemia of the left ventricle, resulting more from the enormous increase in the muscle mass than from decrease in the blood supply. Barnes[3] looks on the inversion of the *T* wave as a manifestation of fatigue of the strained left ventricle (see Barnes's monograph for a splendid discussion). In accord with these conceptions is the occasional observation that when very high blood pressure is reduced for a time by splanchnic section the inverted *T* wave may again become upright.

Electrocardiograms indicating bundle-branch block or other varieties of myocardial damage may be present in essential hypertension even though there are no subjective evidences of heart failure and the left ventricle is not dilated. They show that lesions of the myocardium have resulted from coronary arteriosclerosis or other cause, but do not in themselves demonstrate the existence of heart failure at the time.

Circulatory Measurements.—The *cardiac output* in essential hypertension has been investigated on a number of occasions. The matter is of broad interest in connection with the mechanism of the hypertension. Were the mechanism of the hypertension a consequence of primary excitation of the heart—akin to the state of affairs in Graves' disease—one might anticipate increase in cardiac output, at least to such extent as the hyperactivity of the heart were not neutralized by peripheral vasoconstriction. On the other hand, were the high blood pressure due to primary vasoconstriction —a conception now generally accepted—the cardiac output would be decreased to such extent as the rise in peripheral resistance was not overcome by increase in the work of the left ventricle.

Unfortunately, many of the measurements of cardiac output in hypertension were carried out by unreliable methods. (See Grollman[27] for details.) The pioneer measurements of Plesch[55] revealed an essentially normal cardiac output in hypertensive patients. Subsequent studies by Liljestrand and Stenstroem,[44] Hayasaka,[30] and Ernst and Weiss[18] indicated that the cardiac output in essential hypertension is increased above that corresponding to the oxygen consumption of the patient. Contrariwise, Burwell and Smith,[13] Lauter and Baumann,[39] Ringer and Altschule,[57] Weiss and Ellis,[62] Ewig,[19] and Gladstone[24] found that in hypertension without circulatory failure the minute volume is either within or below the normal limits. Using Grollman's acetylene method for measuring the cardiac output, apparently the best available method, Grassmann and Herzog[23] found the minute volume within the normal in 3 patients with essential hypertension, and Kroetz[35] observed the cardiac output to be low in the large majority of hypertensives, although it was elevated in exceptional instances. The weight of evidence therefore indicates that in essential hypertension the cardiac output is most often within or below the normal values corresponding to the oxygen consumption of the patient, and therefore accords with the prevalent conception that the immediate mechanism of the elevation of blood pressure is increase in peripheral resistance. However, further study of the volume of circulation in hypertensive states seems desirable, for it might disclose the participation of different mechanisms in the production of the high blood pressure. Thus, there is one type of hypertensive patient with predominantly symptoms of vasomotor and emotional instability, in whom the pulse pressure is often very high, and in whom one might anticipate an elevated cardiac output. But in interpreting the findings, one must bear in mind that the basal metabolism is often elevated in essential hypertension, which requires a correspondingly greater cardiac output regardless of the mechanism of the hypertension.

Velocity of Blood Flow.—Available evidence indicates that the blood circulates at approximately normal velocity in at least the large majority of instances of essential hypertension without heart failure. Using the radium C method (page 50), Blumgart and Weiss[9] found the arm-to-arm circulation time within normal limits in many hypertensives; in other cases, it was prolonged. Hitzig, King and the writer have made a large number of measurements of the arm-to-lung (ether method) and arm-to-tongue (saccharin method) circulation times in various forms of hypertension, and have found them within normal limits in the absence of heart failure. In unusual instances in which hypertension is associated with polycythemia and marked increase in circulating blood volume (Gaisboeck's type of polycythemia), the circulation time may be moderately prolonged. As pointed out by Blumgart and Weiss, the absence of acceleration of the velocity of blood flow in essential hypertension is of theoretical interest, in that it furnishes further evidence that the elevation of blood pressure is not due to primary overactivity of the heart.

Venous Pressure.—In the large majority of instances of essential hypertension without heart failure, the venous pressure is within normal limits. In exceptional instances, as shown by Blumgart and Weiss,[9] and Brandt and Katz,[12] the venous pressure is elevated to such values as 10 to 12 cm. of water in the absence of other evidences of cardiac insufficiency. I have seen this most often in the malignant phase of essential hypertension. The origin of the elevation of venous pressure in these cases is not clear. Among the factors that may be concerned are constriction of the veins, obstruction to the venous return to the right heart by a bulging interventricular septum (page 447), and increase in circulating blood volume.

Arterial Pressure.—Evidences of heart failure may be entirely lacking despite very high arterial pressure. A woman with arterial pressure of 300/150 mm. was able to walk up three flights of stairs without undue shortness of breath. The relations of the height of the arterial pressure to heart failure will be further discussed in the following (page 445).

Capillary Pressure.—Despite a number of investigations little is known concerning the pressure in the capillaries in hypertension. This is largely due to the fact that the methods for measuring capillary pressure in man are not yet satisfactory. Boas and Mufson[11] found the capillary pressure normal in most instances of essential hypertension, but persistently elevated in other cases. Ellis and Weiss[17] found the capillary pressure in essential hypertension to average 12 mm. of mercury, a slight elevation over their normal average of 9 mm. According to Kylin,[37] the capillary pressure is normal in essential hypertension but elevated in glomerulonephritis.

a finding which has been confirmed by Mufson.[49] On the other hand, Klingmueller[34] did not find any constant difference between the capillary pressure in essential hypertension and in glomerulonephritis.

Circulating Blood Volume.—In some cases of essential hypertension, the circulating blood volume is increased. However, there is no parallelism between the height of the blood pressure and the volume of blood in active circulation, and there are many instances of extreme hypertension with a normal volume of blood in active circulation. Hartwich and May[29] found the circulating blood volume increased in 7 of their 12 cases of essential hypertension. In so-called polycythemia hypertonica (Gaisboeck's syndrome), hypertension is accompanied by polycythemia and consequent increase in circulating blood volume, but the connection between the hypertension and erythrocytosis is not clear. When the heart fails in essential hypertension, the blood volume rises.

Causes of Decompensation of the Hypertensive Heart.—Symptoms of heart failure in essential hypertension generally appear only after the blood pressure has been elevated for years, often decades. Such heart failure is a true decompensation, for it occurs after the left ventricle has previously compensated by hypertrophy and perhaps other mechanisms for the increased work imposed on it by the hypertension. The problem of why the heart finally gives way before the hypertension after coping successfully with it for years is of great importance, and one about which much remains to be learned. Even at the necropsy of a hypertensive patient who has succumbed to heart failure, the judicious observer is often unable to state with assurance why the heart failed.

One factor that is probably of primary significance in the pathogenesis of most instances of heart failure in hypertension is *progressive insufficiency of the blood supply to the left ventricle*. This chamber is forced to perform increased work to master the high blood pressure and hypertrophies in consequence. The bigger muscle mass performing the greater work doubtless requires a more ample blood supply than does a left ventricle of normal size carrying on the usual work. But at the same time as the left ventricle hypertrophies, the persistent hypertension favors the development of coronary arteriosclerosis. In the large majority of instances of hypertension succumbing to heart failure, well-marked coronary arteriosclerosis is found at necropsy. And even in those cases in which the lumen of the coronary arteries is not seriously narrowed, the arteriosclerotic changes in the walls presumably inhibit the *increase* in coronary flow required by the hypertrophic left ventricle. In a number of instances in which great left ventricular hypertrophy due to causes other than hypertension has been present for many years, I have observed that the lumens of the large coronary arteries are con-

siderably bigger than the usual, doubtless an adaptation to more voluminous coronary blood flow. Support for the conception that the blood supply to the hypertensive heart does not keep pace with the hypertrophy is afforded by the finding of Gross and Spark[28] that the average number of arterioles per low power field diminishes in inverse proportion to the weight of the heart.

The underlying basis on which heart failure in essential hypertension develops would thus appear to be relative ischemia of the left ventricle. This results from the coincident operation of two pathogenic factors, namely, hypertrophy of the left ventricle with resultant need for more ample blood supply, and limitation of blood flow to the left ventricle due to arteriosclerosis of the coronary vessels Often, it would seem, the simple progress of these two factors leads to weakness of the left ventricle and the clinical manifestations it entails. But in other cases, the actual appearance of clinical symptoms of heart failure is precipitated by various factors which accentuate the disproportion between the blood flow needed by the left ventricle and that which it actually receives. Among these, the following may be mentioned:

1. *Clinically Manifest Coronary Arteriosclerosis.*—In the foregoing, we have seen that coronary arteriosclerosis is probably one of the underlying pathogenetic factors in most instances of heart failure in essential hypertension. Sometimes, however, the coronary sclerosis produces neither clinical symptoms nor electrocardiographic changes. And exceptionally, even at necropsy, the sclerosis may compromise the lumens of the coronary arteries so little that one would attribute slight significance to it, were there not the greatly hypertrophied left ventricle with its need of an abnormally great blood supply. But in other cases, the coronary arteriosclerosis is so severe that it is obviously the principal and immediate cause of the heart failure The latter may be initiated suddenly by major coronary thrombosis, or by a change in rhythm. Or the coronary artery disease may be revealed by either anginal pains or electrocardiographic evidences of myocardial damage, which, in longstanding hypertension, one is generally safe in attributing to narrowing of the coronary arteries. Averbuck[1] found that severe coronary arteriosclerosis was present at necropsy in 85 per cent of patients with essential hypertension who had heart failure, but in only 10 per cent of hypertensive individuals without cardiac insufficiency. In a large majority of the necropsies that I have seen on hypertensive patients succumbing to heart failure, actual coronary occlusions or extreme narrowing of coronary branches with focal scarring of the myocardium have been present. Such a manifestly coronary origin of heart failure in hypertension appears to be more common in the male. In individuals with both hypertension and diabetes, coronary arteriosclerosis is generally very severe and is

most often the manifest cause of the heart failure. Similar preponderance of the coronary element in the causation of heart failure is more common in the very old than in the relatively young individual with hypertension.

2. *Overexertion* —Not uncommonly, patients with hypertension attribute their symptoms of heart failure to some physical or emotional stress. Most often, careful interrogation elicits antecedent dyspnea on exertion or other symptoms of heart failure to which little attention had been paid. Among the circumstances which may thus bring hitherto disregarded cardiac weakness to the attention of the patients are emotional upsets, lifting heavy weights, climbing stairs, ingesting a heavy meal, and coitus. But it is to be emphasized that such factors merely bring to the surface symptomatically latent heart failure through accentuating the already existing disproportion between the need of the left ventricle for blood and its blood supply.

3. *Infections.*—Occasionally, an acute upper respiratory or pulmonary infection in a previously well compensated individual with hypertension is followed by heart failure. This may occur during the febrile period, or become manifest only after the patient leaves bed. The factors discussed on page C60 are presumably concerned in the production of the heart failure It may also be thought that the infection injures either the heart muscle directly or in some way affects the arteriosclerotic process in the coronaries adversely; but I am not acquainted with precise anatomical studies in this regard In my experience, the number of instances of heart failure in hypertension which have been definitely precipitated by an intercurrent infection has been very small Hypertensives often pass through severe infections, such as lobar pneumonia or typhoid fever, without developing circulatory failure. Moreover, it should be borne in mind that bronchopneumonia is often a *consequence* of left heart failure (page 244), indeed much more often, I believe, than it is a *cause* of cardiac insufficiency.

4. *Superelevation of the Blood Pressure.*—There is no close correlation between the height of the blood pressure in essential hypertension and the liability to heart failure. In relatively young individuals in whom essential hypertension enters the malignant phase, the arterial pressure, especially the diastolic, is usually very high, and yet they almost always succumb to renal insufficiency with the cardiac manifestations in the background of the clinical picture. Especially in middle-aged women just past the menopause it is not uncommon to observe systolic pressure over 250 and diastolic pressure over 130 for several years with little cardiac enlargement and no marked evidences of heart failure. On the other hand, heart failure may develop with a blood pressure which has not exceeded 170/100 mm. In exceptional cases with widely fluctu-

ating blood pressure, an abrupt and marked rise of blood pressure seems to precipitate acute left ventricular failure, sometimes with resultant pulmonary edema. This sequence of events has also been observed in true paroxysmal hypertension due to chromaffin tumors of the suprarenal medulla. That most instances of acute left ventricular failure with pulmonary edema in essential hypertension are precipitated by a superelevation of the blood pressure has not been proved, but it is possible (Chapter XIV). In this connection, it should be borne in mind, left ventricular failure with pulmonary edema often *causes* a secondary rise in blood pressure, probably as a result of asphyxia. When overexertion induces left ventricular failure in hypertension, the increase in minute volume is probably a more significant pathogenetic factor than the change in blood pressure; indeed, while severe physical exercise results in elevation of the systolic pressure, the diastolic pressure is either unchanged or falls.

5. *Obesity.*—Individuals with essential hypertension are often obese, and when the adiposity is marked it may play a rôle in the production of cardiac insufficiency. The excessive body weight, of course, increases the work of the heart Also, the upward displacement of the diaphragm due to the enlargement of the omental and other fat depots in the abdomen in most obese persons places the heart in a more transverse position, in which it may work at a mechanical disadvantage Furthermore, in extremely obese individuals there may be extensive deposition of fat under the epicardium with infiltration between the myocardial fibers down to the endocardium. Not uncommonly, symptoms of heart failure in obese patients with high blood pressure are alleviated when the body weight is reduced.

6. *Complicating Valvular Lesions.*—Arteriosclerotic changes in the mitral and aortic valves are common in long-standing essential hypertension Often, they are merely postmortem discoveries, though they may produce systolic murmurs. Less often, arteriosclerotic changes produce aortic diastolic murmurs and very rarely the murmurs of mitral stenosis Such arteriosclerotic valvular lesions seem to play little part in the pathogenesis of heart failure in essential hypertension.

Essential hypertension develops with remarkable frequency in middle-aged women with rheumatic mitral stenosis (page 522). The combination of arterial hypertension and mitral stenosis does not seem especially unfavorable as regards the production of heart failure. I have seen a number of cases in which they have co-existed for years without heart failure. Indeed, it seems plausible that the narrowing of the mitral ostium tends to spare the left ventricle But patients with both mitral stenosis and essential hypertension are much more apt to develop auricular fibrillation than those

with only high blood pressure. When heart failure is initiated with auricular fibrillation in an individual with high blood pressure, the possibility of occult mitral stenosis should be borne in mind, even though characteristic murmurs are not audible during the period of rapid heart action.

The association of essential hypertension with aortic regurgitation of rheumatic or syphilitic etiology is not as common as with mitral stenosis, but is not rare. While some of the cases do well for a considerable time, those due to syphilis are especially apt to develop rapidly progressive heart failure, and sudden death is common, most often as a result of the syphilitic involvement of the mouths of the coronaries.

7. *Emphysema.*—Many elderly patients with essential hypertension have well-marked pulmonary emphysema. In some cases this is merely a "functional" emphysema, due to the failure of the left side of the heart (page 427) But in other cases there is true emphysema It is to be presumed that the latter inflicts an added burden on the right heart. Not rarely, in these patients, circulatory insufficiency starts as right ventricular failure, indicating that the pulmonary disease is concerned in its causation Conceivably, the increased resistance in the pulmonary circuit may serve to shield the left heart to some extent

The Stage of Isolated Left Ventricular Failure.—In the large majority of instances, circulatory failure in hypertension is initiated as isolated insufficiency of the left ventricle

Symptoms.— *Dyspnea,* either exertional or paroxysmal, is by far the most common initial symptom of left ventricular failure in essential hypertension, and may dominate the entire clinical course. Most often, the patient first notices that he is short of breath on climbing stairs, after a heavy meal, during a lively conversation, etc Or orthopnea is the initial complaint, discomfort necessitating the use of more than one pillow, this is especially common in the obese In still other individuals, especially those of sedentary habit, the first subjective evidence of heart failure is awakening at night with a paroxysm of cardiac asthma, or one of its equivalents (page 147) But in such cases with seemingly initial cardiac asthma careful inquiry usually elicits previous shortness of breath on exertion, to which little attention had been paid or which had been referred to obesity or lack of exercise. Rarely, the first attack of cardiac asthma is accompanied by massive pulmonary edema and may be fatal

Patients, even when physicians, use many analogies to describe the purely subjective sensation of dyspnea, and when the description is atypical it may be difficult to decide whether the thoracic, cervical, or epigastric discomfort induced by exertion is dyspnea or angina pectoris, *i e*, whether the symptom is respiratory em-

barrassment due to weakness of the left ventricle or the pain of myocardial ischemia produced by the coronary narrowing so common in hypertension. The differentiation is an important one, especially for rational therapy, but unfortunately cannot invariably be made with certainty. Doubtless, dyspnea and angina pectoris are often combined to form a complex sensation.

Dyspnea may be accompanied by other symptoms of pulmonary engorgement. Of these, *cyanosis* is the most frequent, but is by no means constant. Hypertensive patients of plethoric habitus and with a high hemoglobin content of the blood have cyanotic lips and less often nailbeds with relatively slight degree of pulmonary engorgement; many of these individuals with *habitus apoplecticus* have a color simulating cyanosis even in the absence of heart failure. Another common symptom is *cough*, either dry or productive. The expectoration may be blood-streaked. In an individual with high blood pressure who develops cough, expectoration, and hemoptysis, the first thought should be of left ventricular failure rather than of emphysema, "chronic bronchitis," or other primary pulmonary disease.

Exceptionally, there are episodes of *syncope* or other symptoms of cerebral ischemia. These are much more apt to occur with concomitant well-marked cerebral arteriosclerosis. Insomnia is often an early symptom of left ventricular failure, and is usually alleviated when the heart improves.

Objective Findings.—The heart is usually enlarged downward and to the left. However, there are many cases with severe symptoms of left ventricular failure in which this enlargement cannot be demonstrated by physical examination alone, especially when there is emphysema Sometimes, in an individual previously known to have had a heaving apex beat, this is found less powerful and more diffuse. The auscultatory findings are not always significant. Usually, the heart rate is accelerated, but especially in hypertension there may be severe left ventricular failure with a pulse rate of 80 or less per minute. The first sound at the apex may be less booming than during the compensated stage. Gallop rhythm is the most characteristic auscultatory sign of left ventricular failure; but there are many cases in which it is not heard. An apical systolic murmur is usually present, although without knowledge of the previous findings it may be difficult to determine whether this is functional and a consequence of the ventricular dilatation or due to arteriosclerosis of the mitral valve The pulmonic second sound is accentuated, and may be louder than the likewise intensified aortic second sound Very rarely, especially when renal insufficiency has resulted in anemia, the murmur of aortic incompetence appears.

Inspection, percussion, and auscultation of the chest may reveal the "functional emphysema" stressed by Weiss and Robb (page

427). In such patients the excursions of the lung margins during deep breathing are limited. The small moist râles of pulmonary engorgement may be audible at the bases posteriorly. Not rarely, diffuse squeaks are heard; they evidently result from engorgement, for they disappear with improvement of the heart. The engorgement may be sufficiently intense to produce, *per se*, dulness at the bases in the absence of pneumonic consolidation or pleural effusion.

In sharp contrast to the evidences of pulmonary engorgement is the absence of systemic venous stasis, the cervical veins are not unduly filled, the liver is not enlarged, and edema of the feet is absent.

The effect of left ventricular failure on the arterial *blood pressure* is variable. Most often, there is little change or a moderate fall. Not rarely, however, the arterial pressure rises during acute left ventricular failure (page 149) A severe and rapid fall in arterial tension should always call attention to the possibility of coronary thrombosis with its attendant shock

Alternation of the heart with pulsus alternans occurs most often in the left ventricular failure of hypertension It is especially apt to development in the malignant phase of essential hypertension after renal insufficiency has appeared.

Roentgen-ray Examination.—Roentgen-ray examination reveals the increase in size of the left ventricle, which is enlarged downward and most often, but not always, to the left Weiss and Robb[63] call attention to the fact that the excursion of the left border is less than that of the right ventricle, this is a necessary consequence of dilatation of the left ventricle (page 375). There may be some bulging of the left auricle into the retrocardiac space, but it is not as marked as in many cases of mitral stenosis and is indeed most often not demonstrable Prominence of the pulmonary conus may reveal the hypertrophy of the right ventricle. The hilus shadows and lung fields exhibit the characteristics of engorgement.

Electrocardiogram.—The electrocardiogram does not necessarily exhibit any deviation from that present in the compensated stage of essential hypertension It is to be emphasized that severe left ventricular failure may exist in the absence of electrocardiographic evidences of myocardial damage. When serial electrocardiograms are available, one often finds that the electrocardiogram is essentially the same as when the patient had no symptoms of heart failure. In other cases, new evidences of myocardial damage have appeared, notably lowering of the voltage of the *Q–R–S* complex, defects of intraventricular conduction, or inversion of the *T* wave in the first lead (but see page 436 regarding the latter). However, there may be severe left ventricular failure despite high voltage and upright *T* waves.

The arm-to-arm *circulation time* is almost always prolonged; this

is an important diagnostic aid in obscure cases. We have already referred to the very rare instances of left ventricular failure with normal pulmonary circulation time (page 57). The arm-to-lung circulation time is normal in some cases, prolonged in others (page 210).

The venous pressure is most often normal, exceptionally somewhat high (page 448).

Hypertensive patients with left ventricular failure are always in danger of the three major *complications* of pulmonary engorgement, namely, pulmonary edema, pulmonary infarction, and bronchopneumonia.

The *duration* of the stage of isolated left ventricular failure in essential hypertension is very variable. Often, it lasts for years with exacerbations and remissions. I have known hypertensive patients who have suffered severe episodes of left ventricular failure during a period of ten or more years. There are many individuals with high blood pressure who are mildly or moderately dyspneic on exertion for many years without exhibiting any evidence of failure of the right heart.

The Stage of Combined Left and Right Heart Failure.—Many hypertensive patients succumb during the stage of isolated left heart failure as a result of coronary thrombosis, acute pulmonary edema, cerebral hemorrhage, uremia, bronchopneumonia, or other complications But an even larger quota sooner or later develop insufficiency of the right side of the heart in addition to their preexistent left heart failure.

Pathogenesis of Right Heart Failure in Hypertension.—When the left side of the heart fails the tension in the pulmonary circuit is elevated. The work of the right ventricle is correspondingly increased with resultant hypertrophy As long as the hypertrophied right ventricle masters the increased resistance in the pulmonary circuit, the clinical picture is that of isolated failure of the left ventricle, and engorgement of the venæ cavæ and their tributaries is absent. But sooner or later, in most instances, the right ventricle decompensates; *i. e.*, it fails to empty as completely as before, the tension within the chamber during diastole rises, and engorgement of the systemic veins is the consequence.

The pathogenesis of decompensation of the right ventricle in hypertension is probably often similar to that of the antecedent failure on the left ventricle. The increased tension in the pulmonary circuit and the resultant hypertrophy of the right ventricle necessitate a more ample coronary flow to the right ventricle than in health. But at the same time, progressive arteriosclerosis of the coronary branches to the right, as well as the left, side of the heart interferes with the delivery of such an increased blood supply, until a point is reached at which the blood supply is insufficient and

decompensation occurs. It is true that gross ischemic lesions of the right ventricle as a result of coronary arteriosclerosis are much less prominent than those of the left ventricle (page 453), but there can be no doubt that in widespread coronary arteriosclerosis, the nutrition of the right ventricle must also suffer The secondary causes of decompensation of the left ventricle enumerated on page 440 may likewise operate in causing subsequent insufficiency of the right side of the heart. Many individuals with hypertension develop marked pulmonary emphysema, which serves further to increase the work of the right ventricle. Likewise, the protracted and severe cough often present in the pulmonary engorgement of left ventricular failure adds to the strain of the right side of the heart. Not rarely, the development of auricular fibrillation or another arrhythmia precipitates the insufficiency of the right side of the heart. Flaxman[22] found that auricular fibrillation preceded and seemed to be concerned in the precipitation of about one-quarter of his cases of right heart failure in hypertension.

Displacement of the Interventricular Septum.—Another mechanism producing engorgement of the systemic veins in left ventricular dilatation was described by Bernheim,[7] and is known in the French literature as the *syndrome of Bernheim* In a large number of cases in which hypertension and arteriosclerosis had resulted in great dilatation of the left ventricle, and which succumbed with severe engorgement of the systemic veins, Bernheim observed at necropsy that the right ventricle was not dilated In these cases, he found that the cavity of the right ventricle was greatly compromised by the bulging into it of the greatly hypertrophied interventricular septum. In the course of the dilatation of the left ventricle, the interventricular septum bulged convexly to the right so far as to approach within a few millimeters of the right wall of the right ventricle in the apical half of the chamber. In some of his cases, little more than the upper half of the right ventricular cavity and the pulmonary conus remained open, the apical half of the right ventricle being represented only by a narrow slit between the bulging septum and the lateral wall The pulmonary conus and the right auricle were dilated

Bernheim's conception is that the bulging of the septum into the right ventricle, due to the dilatation of the left ventricle, so obstructs the flow of blood from the right auricle as to produce engorgement of the venæ cavæ with its consequences in the form of swelling of the cervical veins and liver, dropsy, etc. He observed that in these cases, contrary to mitral disease, the systemic venous engorgement is not accompanied by marked congestion of the lungs Apparently, the interference with the filling of the right ventricle by the bulging septum served to protect the lungs from the engorgement which would otherwise have resulted from the failure of the

left ventricle. Observations and deductions similar to those of Bernheim have been published by Mazzei[48] and others.

At many necropsies on patients with hypertension or aortic insufficiency and severe systemic venous stasis, I have also observed that the septum of the enormously hypertrophied and dilated left ventricle bulged so far to the right that a large part of the cavity of the right ventricle was obliterated. These postmortem appearances have often seemed to me to support strongly Bernheim's view that the bulging septum had actually interfered with the filling of the right ventricle during life, especially in view of the great thickness and usual firmness of the septum. Moreover, when the left ventricle fails and dilates the diastolic tension within it rises (page 302), which would further increase the resistance offered by a bulging septum to the filling of the right ventricle.

It is interesting that a similar conception was attained by Henderson and Prince[30a] in an experimental investigation on the perfused heart. They found that when they increased the filling pressure of the left ventricle and thereby dilated and augmented the output of this chamber, the output of the right ventricle fell, a phenomenon which they attributed to displacement of the interventricular septum so as to interfere with the filling of the right ventricle

Septal bulging would explain the occasional cases in which left ventricular dilatation due to hypertension or aortic insufficiency is accompanied by systemic venous engorgement in the absence of severe pulmonary congestion. In a number of patients with hypertension, I have observed elevation of the venous pressure to 12 or even more centimeters of blood in the absence of notable pulmonary engorgement and where the pulmonary circulation time was within or close to the normal. In some of these cases, the roentgen picture revealed enlargement of the left ventricle but little of the right ventricle. It would seem very probable that in such cases the venous engorgement was due to bulging of the septum into the right ventricle, a virtual tricuspid stenosis.

It would thus appear that two mechanisms may result in systemic venous engorgement in essential hypertension:

1. Increase in tension in the pulmonary circuit due to failure of the left ventricle with secondary failure of the right ventricle. Here, the lungs are intensely engorged and the right ventricle is dilated.

2. Bulging of the septum of the hypertrophied and dilated left ventricle into the right ventricle with resulting obstruction to the flow of blood from the right auricle. Here, pulmonary engorgement is less prominent and the right ventricle is not dilated apart from the pulmonary conus and subjacent to the tricuspid valve.

Further investigation is needed to ascertain the relative frequency of these two forms of systemic venous engorgement in essen-

tial hypertension, and the factors leading to the one or the other. It has seemed to me that obturation of the right ventricle by septal deviation is more common in the relatively young, in whom hypertrophy of the left ventricle is more pronounced and the dilatation is more of the "tonogenous" variety (page 304) On the other hand, dilatation of the right ventricle is usually the outstanding factor in long-standing hypertension in the elderly with severe coronary arteriosclerosis, in whom the hypertrophy of the left ventricle is not so great and its dilatation predominantly "myogenous" (page 304) in origin.

Clinical Picture.—When insufficiency of the right heart appears in essential hypertension, the clinical manifestations are much the same as in mitral disease and other forms of right heart failure secondary to weakening of the left side of the heart. Cyanosis, swelling of the veins, rise in venous pressure, the ventricular form of the venous pulse, enlargement, tenderness and pulsation of the liver, subcutaneous edema, hydrothorax, ascites, oliguria, and albuminuria may be present in various combinations. On the other hand, the dyspnea and orthopnea which dominated the picture during the stage of isolated left heart failure are often alleviated, presumably as a result of diminution in pulmonary engorgement And patients who have suffered from nocturnal paroxysms of cardiac asthma frequently lose these entirely or largely with the appearance of systemic venous engorgement The same is most often true of anginal pains, when these were previously present. In other words, with the weakening of the right heart, the patient's suffering may become less intense even though he is now continuously bed-ridden and his outlook worse.

Various changes in the size and shape of the hypertensive heart may accompany the appearance of systemic venous stasis. As mentioned above (page 448), there may be little broadening to the right, these are presumably the cases in which septal deviation is largely responsible for the venous engorgement. In other cases, the cardiac silhouette extends almost as far to the right as to the left as a result of dilatation of the right ventricle and auricle. In these universally dilated hearts, the amplitude of pulsation of the borders is very small and may be hardly perceptible

Not rarely, heart failure in hypertension runs its entire course with little change in *rhythm*. Other cases, however, exhibit disturbances in rhythm. Of these, only alternation is an unequivocal expression of heart failure; the other arrhythmias may also occur in the absence of failure, being largely the result of myocardial damage due to coronary arteriosclerosis. Extrasystoles and auricular fibrillation are the most common arrhythmias in hypertensive patients; the latter occurred in 75 of Rothstadt's[58] 1000 cases of hypertension and in 158 of 623 patients with hypertensive heart

disease studied by Flaxman[22] Paroxysmal tachycardia is not rare; it may precede the onset of heart failure by many years, or the latter may never develop. Auricular flutter may also occur. When coronary disease produces heart block in a hypertensive patient, the previously high diastolic pressure may fall as a result of the long diastole while the systolic tension remains high.

Left Ventricular Failure in Acute Glomerulonephritis

In acute glomerulonephritis, there is often quick and marked rise in arterial pressure, which is doubtless primarily the result of widespread peripheral vasoconstriction. In severely oliguric or anuric patients, hydremia with resultant increase in the volume of circulating blood may also add to the work of the heart, but further studies are needed to ascertain how often this factor is significant; the few available investigations indicate that hydremia is present in only some of the cases. Pleural or peritoneal effusions may hamper the work of the heart. Convulsions occasion a terrific strain on the heart While the myocardium usually exhibits few histological changes at necropsy, it is to be presumed that in the cases in which activity of the causative infection is documented by fever or other evidence, the functional capacity of the heart muscle may be adversely affected Injury to the heart muscle in acute glomerulonephritis is not uncommonly indicated by electrocardiographic changes (Master, Jaffe and Dack[47]), though these are usually but slight and evident only in serial tracings.

As a result of these factors, evidences of left ventricular failure are very common in acute glomerulonephritis. The outstanding symptoms are dyspnea and sometimes palpitation or discomfort when lying on the left side. Dyspnea may be an initial symptom of acute glomerulonephritis. Objectively, the findings are tachycardia, perhaps slight enlargement of the left ventricle, and often a systolic murmur at the apex and gallop rhythm. The weakness of the left ventricle may be indicated by the fact that the pulmonic second sound is louder than the aortic second sound despite the presence of hypertension.

In rather exceptional cases, cardiac insufficiency becomes very severe and dominates the clinical picture; the chief danger to life in the first few days of acute glomerulonephritis is heart failure. The heart may give way with startling suddenness, either out of a clear sky or following a convulsion. At the onset, the picture is generally that of typical left ventricular failure. There is agonizing dyspnea and orthopnea, and cyanosis may be superimposed on the previous pallor of the patient. The heart rate becomes very rapid, there is gallop rhythm and a functional systolic murmur at the apex, and the pulmonic second sound becomes accentuated; sometimes, enlargement of the left ventricle can be demonstrated within

a relatively brief period. Moist râles are generally to be heard at the bases of the lungs and at any time frank pulmonary edema with its characteristic auscultatory signs and pink, foamy, albuminous expectoration may appear. In some instances the blood pressure falls, but more often it rises (page 233) There may be alternation of the pulse. During this stage, there is neither peripheral edema nor notable swelling of the liver, and the cervical veins are not distended except during violent paroxysms of dyspnea Death from pulmonary edema may be appallingly rapid—the hyperacute asystole of the French Some patients present this picture of isolated failure of the left ventricle for days, the dominant feature being either continuous or paroxysmal dyspnea with or without demonstrable pulmonary edema. In other instances, there appear signs of failure of the right ventricle, in the form of swelling of the cervical veins and liver, and cardiac edema. Of course, in these patients it is often difficult to tell whether dependent edema is cardiac or nephritic in origin, both pathogenetic factors may be involved

CORONARY ARTERIOSCLEROSIS

An anachronism in the development of cardiology is the comparatively recent date at which the profession attained a general understanding of so common and often fatal a malady as coronary arteriosclerosis * This tardiness is perhaps to be attributed to the frequency with which advanced coronary disease is found at the necropsy of individuals who had no cardiovascular symptoms—which led to the denial of clinico-anatomical correlations that seemed to exist in other cases—and to the many and diverse guises behind which narrowing of the coronaries is masked. Principal among the latter are the following·

1. **Angina Pectoris.**—Notwithstanding that John Hunter's friends had already convinced themselves that coronary arteriosclerosis produces angina pectoris, the connection was still disputed in the second decade of the present century by no less a master than Clifford Allbutt

2. **Myocardial Infarction.**†—It almost defies understanding that the everyday clinical drama of myocardial infarction was not correctly interpreted until Herrick's[31] classical paper of 1912, despite the

* Dock[16] has recently published an excellent historical survey of coronary occlusion

† The symptoms and signs generally designated as those of coronary thrombosis actually emanate from the resultant myocardial infarction But, as Libman[41] long ago pointed out, by no means all infarcts of the heart are due to coronary thrombosis In a careful investigation, Friedberg and Horn[32] found that 31 per cent of myocardial infarcts were not due to recent coronary thrombosis When the coronary arteries are markedly narrowed, extracardiac causes of diminished cardiac output may result in ischemic necrosis of the myocardium in the absence of thrombosis Indeed, such conditions as aortic stenosis and pulmonary embolism may produce foci of myocardial necrosis with little coronary disease (*cf* also page 622) In general, therefore, as Friedberg and Horn point out and in accord with the customary usage in France, the use of the term myocardial infarction is more accurately descriptive of what is actually diagnosed than is coronary thrombosis.

multitudinous comparative clinical and anatomic studies of the contemporaries of Laennec and Virchow.

3. **Chronic Left Ventricular Failure.**—Only in the past few decades has the profession in general appreciated that the vast majority of instances of left ventricular failure in middle-aged and elderly individuals in which necropsy reveals widespread myocardial fibrosis are due to coronary sclerosis and do not represent the late stage of antecedent inflammation of the heart implied by the formerly usual diagnosis of "chronic myocarditis." The usual onset of the insufficiency of the arteriosclerotic heart with left ventricular failure seems to be a consequence of the fact that ischemic damage to the myocardium due to coronary narrowing affects the left ventricle most severely (page 458). Sooner or later—it may be only after a decade—the right ventricle also gives way and the patient has the usual symptomatology of generalized cardiac failure.

4. **Arrhythmias.**—Symptoms due to extrasystoles, paroxysmal or continuous auricular fibrillation, paroxysmal tachycardia, auricular flutter, or heart block (Stokes-Adams syndrome) may for many years be the only manifestations of coronary arteriosclerosis.

5. **Asymptomatic Coronary Arteriosclerosis.**—As mentioned above necropsy may reveal marked coronary sclerosis, even with old occlusions and myocardial damage, in patients who died from other causes and without a history of cardiac symptoms. Nowadays, since electrocardiography has become a commonplace in routine examinations, one not rarely encounters electrocardiographic changes in all probability due to coronary disease in individuals without symptoms of heart disease.

6. **Sudden Death.**—Coronary arteriosclerosis is the most common cause of "dropping dead." In some such cases subsequent investigation elicits that angina pectoris or other cardiac symptoms had been present. In others, the victim, so far as can be ascertained, had had no symptoms. Necropsy may disclose, in addition to the older changes of coronary arteriosclerosis, either fresh thrombosis which has not yet produced infarction or thrombosis plus infarction. In other cases, only marked coronary narrowing without occlusion is to be found; in the absence of other cardiac or extracardiac cause of death, it is assumed that the coronary disease was responsible, perhaps through the intermediacy of ventricular fibrillation (page 354), though there is no proof of this.

The clinical manifestations just enumerated may occur alone, in combination, or in sequence. Angina pectoris and the arrhythmias are dealt with in other chapters. Because of the frequency of their association, the left ventricular failure of coronary sclerosis is considered in conjunction with hypertension (page 443) and in Chapter XXIV. Peculiar to coronary arteriosclerosis is complication by myocardial infarction.

MYOCARDIAL INFARCTION

With the rarest of exceptions, myocardial infarction involves primarily the left ventricle (*cf.* page 458). I have not seen a large myocardial infarct which was not situated primarily in the left ventricle, although not rarely the infarction extends from the left ventricle and septum to the adjacent portion of the septum; very rarely, the necrosis reaches to the auricles * The consequence is that the heart failure of myocardial infarction is left ventricular failure.

Like other forms of left ventricular failure, that of myocardial infarction tends on the one hand to engorge the lungs and on the other to diminish cardiac output But while the symptomatology of the more chronic forms of left-sided failure due to hypertension, valvular defects or coronary sclerosis is almost entirely that of pulmonary engorgement, with the consequences of decreased cardiac output in the background, the same is often not true of the acute left ventricular failure of myocardial infarction. On the contrary, the symptomatology of myocardial infarction is often completely dominated by the consequences of decreased cardiac output with pulmonary engorgement hardly discernible. One is then confronted by the classical clinical picture of shock The manifestations are practically identical with those of traumatic shock, the circulatory collapse that results from the vomiting of intestinal obstruction or the perforation of a viscus, etc. The difference is one of pathogenesis: in myocardial infarction the decrease in cardiac output which causes the symptoms is of cardiac origin, in traumatic shock of peripheral origin. For this reason the shock of coronary thrombosis is here spoken of as cardiac shock. Myocardial infarction is the paradigm of cardiac shock, however, the same picture of cardiac shock occurs in other forms of acute heart failure, being a consequence of the rapidity with which the heart fails (*cf.* page 653).

Most often, cardiac shock and anginal pain dominate the clinical scene in the first days of myocardial infarction afflicting an individual who did not previously suffer from heart failure. After a few days, the shock tends to disappear and the patient either improves or the evidences of pulmonic and perhaps also systemic engorgement become increasingly prominent. Contrariwise, when the myocardial

* The causes of the greater susceptibility of the left ventricle to ischemic necrosis due to cutting down of the blood supply are not altogether clear They are presumably connected with the greater thickness of the left ventricle, which may render compensatory collateral circulation from the thebesian vessels and other sources less efficient Whitten[44] found that the arteries supplying the right ventricle spread practically in the same plane as the larger vessel from which they arise, while the arteries to the left ventricle leave the main trunks at right angles He believes this anatomical peculiarity tends to immobilize the larger arteries to the left ventricle and thus favors the production of angulations and kinks in consequence of the tortuosity of arteriosclerosis, the angulation and kinking in turn interfere with blood flow.

infarction affects a patient with pre-existent heart failure, the evidences of shock and of pulmonary and sometimes systemic engorgement are most often commingled from the start. In the latter type of case, the element of shock may be completely absent. We shall first discuss the clinical pictures of shock and of pulmonary and systemic engorgement due to myocardial infarction, and then their pathogenesis

Clinical Picture of Cardiac Shock Due to Myocardial Infarction.—Shock may appear almost simultaneously with the pain that signals the occlusion. In other cases, evidences of circulatory failure first appear hours or even days after the infarction. Needless to say there are also many cases in which clinical or electrocardiographic evidence proves the presence of infarction in which there are no indications of circulatory failure. It is the cases of myocardial infarction with abdominal pain and simultaneous shock that the unwary occasionally mistake for perforation of a peptic ulcer or other intra-abdominal episode, the shock symptoms may be essentially the same in both instances One should bear in mind that there are many cases of myocardial infarction with little or no pain* in which the pain is that of shock. Indeed, according to Libman,[43] shock is more apt to occur in hyposensitive individuals who experience little or no pain with the attack

The symptoms of shock are the classical ones described in Chapter XXXII. In addition to precordial pain, its equivalents and radiations, weakness, nausea, vomiting, thirst, profuse sweating, and coldness of the extremities are common complaints. While there are rare instances in which the onset of coronary thrombosis is with loss of consciousness presumably due to cerebral ischemia, the mind is generally clear, unless benumbed by morphine. Restlessness and excitement often develop, and on rare occasions progress to delirium. The patient most often can lie flat in bed without orthopnea, although he may complain of dyspnea and breathe fast and superficially. The absence of orthopnea is in contrast to what occurs in the cases with heart failure. Cheyne-Stokes breathing is not rare, especially if morphine has been administered, but the phasic variations are not striking until the terminal stages. The skin is pale and clammy; the perspiration may be so profuse as to soak the clothing, a feature very characteristic of shock. The features are often sunken The face and hands often exhibit a grayish cyanosis that may lead to the suspicion of the diagnosis at the first glance. Patches of irregular bluish-red mottling (cutis marmorata) may be present. The hands and feet are cold, especially, as emphasized by Levine,[39] in contrast with the rectal temperature, which is

* Gorham and Martin[44] found pain to be absent in 42 of 100 fatal cases of coronary occlusion, in 98 of which there were gross infarcts This incidence of painless fatal coronary occlusion is higher than my experience. Gorham and Martin state that painless myocardial infarction is more common in the older age groups and that the location of the infarct bears no relation to the presence or absence of pain

generally elevated. If there is considerable fever, the hands and feet may not feel cold, though they are not as warm as one would anticipate from the pyrexia present.

The *heart* is usually not enlarged above the dimensions present prior to the infarction The rate is rapid apart from the unusual instances of heart block. Extrasystoles, continuous or more often paroxysmal auricular fibrillation, auricular flutter, ventricular tachycardia, nodal rhythm, shifting pacemakers, and the other arrhythmias which may occur, as well as the pericardial rub that can be heard at one time or another in perhaps one-quarter of the cases, will not be discussed here; details can be found in Levine's[39] monograph. The heart sounds generally seem distant, and there may be embryocardia However, the most common auscultatory sign is gallop rhythm, which is present at one time or another in most cases, and often suffices for immediate differentiation from gallstone colic or other confusing conditions Gallop rhythm may be the one physical sign pointing unequivocally to cardiac injury.

During the stage of shock, physical and roentgen examination of the lungs may reveal little that is abnormal It is true that Blumer[8] failed to detect pulmonary signs in only 17 of 76 patients with coronary thrombosis However, these findings pertain to the totality of clinical types of myocardial infarction, the proportion with negative pulmonary findings is much higher in the first days of initial myocardial infarction In some cases with an otherwise characteristic picture of shock, small râles appear very early at one or both bases. The origin of these râles is not clear, they also often appear in other forms of shock not of cardiac origin (notably, surgical shock). Slight degrees of pulmonary engorgement may be concerned in their pathogenesis, or, since the patients most often breathe superficially, there may be an element of atelectasis Nor is it clear why the râles are most often on the left side, there is no acute enlargement of the heart to compress the left lower lobe, and pleuropericarditis does not seem to be the explanation During the stage of shock there is little or no orthopnea and the pulmonic second sound is not accentuated, indicating the absence of hypertension of the lesser circulation. In accord with the paucity of signs of pulmonary engorgement during the period of shock, Hitzig, King and the writer[21] found that *the velocity of blood flow through the lungs is slowed little or not at all* This was demonstrated by the injection of saccharin (page 51); in cases of myocardial infarction with the picture of pure shock the circulation time thus measured proved to be close to or within normal limits Subsequently, as the shock clears up, pulmonary blood flow may become retarded, then, symptoms and physical signs of marked pulmonary engorgement make their appearance. The susceptibility of patients with myocardial infarction to bronchopneumonia is well known, but this dreaded

complication does not usually appear until a later stage after pulmonary engorgement has set in.

The *pulse* is small and rapid, apart from the rare cases of heart block. Levine[39] states that alternation of the pulse is common, but in my experience it has been extremely rare.

In the large majority of instances, the *arterial pressure* falls sharply from its previous level. If, as is often the case, hypertension was previously present, the tension may still be above the normal. The height of the blood pressure is of considerable prognostic importance; sharp fall in tension is of serious omen, and the outlook is grave when the systolic pressure falls below 80 mm. In exceptional cases, the arterial pressure does not fall and may even rise (*cf.* Weiss[61]), although the presence of shock is amply attested by cold extremities, gray cyanosis and sweating; evidently, as may also occur in other forms of shock, compensatory vasoconstriction atones for the decreased output of the heart (page 622).

The superficial *veins* are collapsed and the *venous pressure* as measured in the antecubital veins is low (for figures *cf.* Fishberg, Hitzig and King[21]) The writer formerly regarded the low pressure in the veins of the extremities as evidence of the presence of peripheral circulatory failure However, it appears that this interpretation is incorrect, and that the poor filling of the veins of the peripheral veins is merely a consequence of arteriolar constriction in the extremities reflexly evoked by the diminished cardiac output. This arteriolar constriction subserves the compensatory functions of maintaining the arterial pressure and deviating blood toward the more immediately vital organs (Chapter XXXII). The collapsed veins of the extremities may be in striking contrast to the distended veins of the neck (page 656).

Peripheral *edema* is absent.

The *liver* is not enlarged in patients with this clinical picture. In myocardial infarction, upper abdominal pain, tenderness and rigidity are not necessarily indicative of hepatic engorgement, but are often "reflex" manifestations of the cardiac lesion and perhaps sometimes correlated with pericarditis Enlargement of the liver occurs only when the right side of the heart has given way (page 459). The most common abdominal finding during the stage of shock is tympanites, which is often marked and troublesome.

Oliguria is present and may attain anuria. In severe cases, the result is often azotemia (page 623)

The *electrocardiographic findings* are mentioned briefly on page 459; excellent discussions have been given by Barnes,[2] Wood and Wolferth,[63] and Wilson [66] For a description of the fever, leukocytosis, embolic phenomena, pericarditis, and other manifestations, the reader is referred to Levine[39] and Levy.[41] Here it may be pointed out that the fever is probably not merely a manifestation of necrosis

of the heart muscle; the fact that the extremities feel relatively cool in comparison to the rectal temperature indicates that the diminished blood flow through the skin favors pyrexia through decreasing heat loss.

The duration of shock in myocardial infarction is generally not long. Within a few hours to several days, the symptoms of shock start to clear up, and the patient either improves or the manifestations of pulmonary and perhaps also systemic venous engorgement appear. There are, however, exceptional cases in which the patient remains in a state of shock with grayish cyanosis, clammy skin, cold extremities, and low venous pressure for two weeks or more. In some such cases that I have seen there have been electrocardiographic or anatomical evidences of extending necrosis of the heart muscle or fresh thrombosis Sometimes, the development of bronchopneumonia seems responsible for the protraction of shock.

Pulmonary and Systemic Venous Congestion in Myocardial Infarction.—Doubtless, myocardial infarction sufficiently extensive to affect the dynamics of the left ventricle always entails at least slight pulmonary engorgement But we have just seen that in many cases of myocardial infarction with the clinical picture of shock the evidence of accumulation of blood in the lungs are in the background and may be hardly detectable. Under other circumstances, on the contrary, the shock is accompanied by the consequences of pulmonary and perhaps also systemic venous engorgement, or the latter may completely predominate. Thus, in rare instances coronary thrombosis quickly proves fatal as a result of intense pulmonary engorgement with fulminant pulmonary edema, such cases are among those which the coroner encounters in seeking for the cause of sudden death A common sequence of events is that shock predominates in the first days after the myocardial necrosis, to be followed by the development of pulmonary engorgement The symptoms of congestion of the lungs most often dominate the scene from the very start when coronary thrombosis occurs in an individual already suffering from heart failure as a result of the underlying coronary arteriosclerosis or who has survived previous episodes of infarction. In 43 such patients Hitzig, King and the writer[21] found symptoms of pulmonary and systemic venous engorgement dominant in 32, while in the remainder shock was more prominent

The symptoms of pulmonary engorgement due to coronary thrombosis are the usual ones: dyspnea, orthopnea, cough, hemoptysis, cyanosis, congestive râles, accentuation of the pulmonic second sound, slowing of the circulation time, frequent complication by hemorrhagic infarction or bronchopneumonia, etc Addition of right-sided failure is revealed by engorgement of the systemic veins, swelling of the liver, and edema. Edema, however, is exceptional; it developed in only 5 of the 59 cases studied by Fishberg, Hitzig

and King.[21] A special feature in many of the cases is complication by transitory episodes of shock characterized by weakness, sweating, perhaps vertigo or syncope, pallor, and fall in blood pressure.

Pletnew,[56] Kohan and Budin,[35] and others thought that they were able to infer the site of coronary thrombosis from the type of heart failure present. They reported observations indicating that thrombosis of the left coronary artery with anterior infarction results in left ventricular failure with pulmonary engorgement and enlargement of the heart to the left. On the other hand, they found that thrombosis of the right coronary artery with posterior infarction is characterized by right heart failure with swelling of the veins and liver and enlargement of the heart to the right. Hitzig, King and the writer[21] did not find such differentiation feasible. Our clinical and necropsy observations revealed that either anterior or posterior infarction can cause engorgement of the lungs alone or combined left and right ventricular failure. And when shock dominates, the venous pressure is low in either anterior or posterior infarction Because of these observations, it does not seem to us that the type of circulatory failure present permits, *per se*, the differentiation between anterior and posterior infarction.* However, Libman[42] has

* It is not surprising that the cardiac insufficiency of myocardial infarction always includes left ventricular failure, and that right heart failure occurs only in addition to the latter and not alone For, as mentioned above, the infarction practically always implicates principally the left ventricle. Infarction of the right ventricle alone is so rare as to constitute a curiosity (Barnes[3] mentions an instance of infarction confined to the right ventricle and Karsner[33] one limited to the right auricle, but I have not encountered either) The two most common localizations of massive infarcts are the following (1) When the thrombosis is in the system of the left coronary artery, the infarct is most often situated in the anterior and apical portion and often extends far enough to the right to implicate the anterior third of the septum and the adjacent anterior and apical portion of the right ventricle ("anterior infarction"), (2) if the right coronary artery or its tributaries are occluded, the infarct is located in the territory of the posterior and basal portion of the left ventricle, the posterior two-thirds of the septum, and the adjacent posterior surface of the right ventricle and auricle ("posterior infarction") Much less common is infarction of the lateral wall of the left ventricle due to occlusion of the left circumflex branch ("lateral infarction") This description of the relation of the site of occlusion to the location of the resulting infarction has become classical, but is actually an oversimplification As is shown with especial clarity by the beautiful injection studies of Blumgart[16] and his collaborators, multiple occlusions and narrowings of both coronary arteries are most often concerned in the pathogenesis of massive infarction Their observations show that the portion of the left ventricle previously supplied by one coronary artery may be maintained in good nutrition by the development of collateral circulation from the other coronary. In consequence, infarction may first be precipitated by fresh occlusion of the coronary artery that does not normally supply the infarcted area but which furnished the collaterals Under such circumstances, for example, fresh occlusion of the right coronary artery may precipitate anterior infarction Anomalous distribution of the coronaries and almost simultaneous multiple thromboses, neither of which is rare, further complicate the relation of the sites of occlusion and infarction.

As stated in the text, the findings on physical examination do not permit differentiation of anterior and posterior infarction, apart from the unusual instances in which development of heart block indicates posterior infarction (*cf* Master, Dack and Jaffe[46]) Pericardial infarction may be audible in posterior as well as anterior infarction. Perforation of the septum can usually be recognized by the sudden

found that when the liver becomes greatly enlarged within a few hours after the onset of myocardial infarction, the right coronary artery is the one affected.

In those of the patients studied by Hitzig, King and the writer[21] in whom severe right heart failure and high venous pressure developed after coronary thrombosis, and who then came to necropsy, extensive infarction of the interventricular septum was present. Such septal infarction may be part of either anterior or poster or infarction. It is conceivable (but only a suggestion) that in such cases, in addition to the motor weakness, herniation of the necrotic septum into the cavity of the right ventricle with resultant obstruction to diastolic filling is concerned in the production of the venous engorgement. Whether the rapid development of high venous pressure following coronary thrombosis is always indicative of septal infarction must be studied on larger material. However, it is to be reiterated that even with extensive septal infarction the venous pressure in myocardial infarction is low if shock dominates the scene.

Factors Influencing the Form of Left Ventricular Failure in Myocardial Infarction.—The left ventricular failure of myocardial

development of a rough systolic murmur and thrill over the area of the right ventricle in a patient with coronary thrombosis, but such perforation may occur in either anterior or posterior infarction However, the studies of Barnes and Whitten,[4] Parkinson and Bedford,[54] Pardee and Bell,[63] Crawford[16] *et al*, Wilson[67] *et al*, and Wolferth[63] *et al* have shown that electrocardiographic differentiation of the two is feasible in most instances (31 of 40 cases studied by Fishberg, Hitzig and King[21])

In anterior infarction, the *RS–T* segment is elevated above the isoelectric level in the first and often the second leads, and the subsequent inversion of the *T* wave with the frequently upwardly convex descending limb (coronary *T* of Pardee,[62] cove plane *T* of Oppenheimer and Rothschild[61]) develops in these leads On the other hand, in posterior infarction the *RS–T* interval is elevated above the base line in the third and perhaps also the second leads and the subsequent changes in the *T* wave develop in these leads. In anterior infarction a significantly large *Q* wave often develops in the first lead, in posterior infarction in the third lead (Wilson[67] *et al*) From the studies of Fenischel and Kugell,[30] it would seem that the appearance of a large *Q* wave in the third lead indicates that the lesion has involved the posterior portion of the septum Similarly, it is probable that the development of a large *Q* wave in the first lead bespeaks implication of the anterior portion of the septum In the cases that I have had the opportunity to check at postmortem, these interpretations have held true

The great value of electrocardiography with precordial leads for the diagnosis of myocardial infarction has been shown by Wolferth and his associates The significance of the findings with precordial leads for the localization of the infarct is also considerable In anterior infarction, Wood[44] and his co-workers found the following changes The initial positive deflection disappears or is markedly diminished in size, the *RS–T* interval is elevated, and the *T* wave becomes inverted and sometimes huge (over 13 mm). In posterior infarction, the precordial lead may show little change In other instances, the *RS–T* interval is depressed, especially if the chest electrode is placed in the left anterior axillary line, and there may be stunting or even disappearance of the initial positive deflection There may be a huge upright *T* wave It would seem likely that future investigation will reveal multiple precordial electrocardiography as the most accurate means for localizing myocardial infarction

Wood, Wolferth and Bellet[43] have found that infarction of the lateral wall of the left ventricle is characterized by depression of the *RS–T* interval in the precordial lead and often also in the first and second leads without characteristic changes in the third lead

infarction is manifested on one side by pulmonary engorgement and on the other by decreased cardiac output with resultant shock. *But the relative importance of these two groups of symptoms varies* greatly in individual cases. In some patients the symptoms of shock are so much in the ascendant that the picture differs little from that of traumatic shock. In other cases, the manifestation of *pulmonary and perhaps systemic venous engorgement dominate* the symptomatology so completely that it is all but identical with that of decompensation due to valvular disease. In Harrison's terminology, in the one patient forward failure predominates, in the other backward failure is in the ascendant, in still others they are commingled in various degrees and sequences. With regard to the pathogenesis of these differences, the following facts seem pertinent:

1. The almost pure picture of shock is encountered most often when major myocardial infarction occurs in an individual who had no previous heart failure, although he may have suffered from angina pectoris.

2. The symptoms of pulmonary and perhaps systemic venous congestion usually predominate when myocardial infarction afflicts an individual who already had heart failure as a result of coronary sclerosis and often also hypertension.

3. Precisely the same clinical picture of shock is encountered in other forms of heart failure of abrupt onset in individuals who previously had little or no cardiac insufficiency. Examples are acute right heart failure due to pulmonary embolism, some cases in which the onset of auricular fibrillation or other disturbance in rhythm abruptly cuts down the cardiac output, rapid tamponade of the heart by hemopericardium or purulent pericarditis, and obstruction of the stenotic mitral valve by a ball valve thrombus.

4. Comparison of the circulating blood volume in the cases with the picture of shock and those in which passive congestion of the lungs and perhaps also of the systemic veins predominates, discloses an interesting difference. In cases of myocardial infarction with the clinical picture of shock occurring in patients who had not previously had heart failure, Fishberg, Hitzig and King[21] found the blood volume not increased, indeed, it was most often toward the lower limit of normal and rose as the symptoms of shock improved On the contrary, when myocardial infarction resulted in the symptomatology of pulmonary engorgement, the blood volume was *definitely increased*. Such elevation of blood volume was *also* found when myocardial infarction occurred in patients with previous heart failure or hypertension, even though the infarction resulted in shock.

A plausible *working hypothesis to correlate these findings may* be suggested along the following lines: In protracted heart failure the circulating blood volume is increased, the increase subserving

a compensatory function in tending to maintain the cardiac output at a level less depressed than would otherwise be the case Apparently, this increase in blood volume takes a significant time to develop, for when heart failure is induced suddenly by myocardial infarction, the blood volume is not augmented This has the effect, on the one hand, of not causing as much pulmonary engorgement as in equally severe left ventricular failure of gradual onset, but, on the other hand, of producing a more pronounced drop in cardiac output. The result is that the symptomatology is predominantly that due to decreased cardiac output, *i e*, shock or what Harrison terms forward failure. Quite the opposite obtains when myocardial infarction occurs in a patient who previously had heart failure of more or less pronounced degree and duration. Here, the blood volume is increased, with the result that pulmonary and sometimes also systemic venous engorgement plays a more prominent part and decreased cardiac output is less significant.

The thought naturally comes to mind that liberation of histamine-like substances from the infarcted heart muscle may be concerned in the production of shock in myocardial infarction. However, against this conception speak the frequent appearance of shock at the very onset of the infarction and the failure of Fishberg, Hitzig and King[21] to find concentration of the blood. A factor that may be concerned, but is as yet hypothetical, is relaxation of small vessels due to nervous reflexes from the heart

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CHAPTER XXVI

HEART FAILURE INITIATED BY INSUFFICIENCY OF THE LEFT SIDE OF THE HEART: III. AORTIC VALVULAR LESIONS

AORTIC REGURGITATION

AORTIC insufficiency strains the left ventricle and may thus result in classical left ventricular failure. Dynamically significant leaks are almost always due to rheumatic valvulitis or to implication of the aortic valve in syphilitic aortitis. Atherosclerotic changes in the aortic ring and cusps often produce a regurgitant murmur, but quantitatively significant leaks are rare. Other forms of regurgitation are discussed on page 473.

Pathological Anatomy.—Rheumatic Aortic Regurgitation.—In rheumatic infection, the aortic valve is implicated with a frequency second only to that of the mitral valve. Histological studies have shown that the process starts as a *valvulitis* within the substance of the cusps, the superficial verrucæ for which one looks at the post-mortem table as evidence of fresh rheumatic activity are secondary developments, which may not be present even though the microscope reveals definite endovalvular lesions According to Klinge,[30] the earliest histological findings consist in foci of fibrinoid change between the collagenous fibers of connective tissue of the cusp. He states that at first the collagen fibers are unaffected, but extensive studies by Dr. Louis Gross[23] indicate that collagen necrosis may occur at a very early stage. Soon there is cellular reaction with proliferation of fixed connective tissue elements and infiltration of wandering cells Granulomata develop which are cytologically akin to the Aschoff bodies of the myocardium (page 340) Rarely, there is diffuse cellular infiltration of the cusps. Over the valvulitis, but selectively and usually first at the closure line of the cusp, the minute elevations known as verrucæ develop. These have generally been considered as formed from blood elements by thrombosis, and the term thrombo-endocarditis often applied to rheumatic endocarditis. However, Gross[23] has shown that this is not always the case; his findings indicate that the verrucæ are more often localized swellings of the subendothelial tissue which is the site of the inflammatory lesions just described That mechanical factors play a significant accessory rôle in the pathogenesis of the verrucæ is shown by their elective localization along the line of closure of the cusps. Rheumatic verrucæ are so small that, *per se*, they are insignificant in the production of regurgitation

It is not known how often and to what extent resorption of such lesions occurs. But when this does not take place, the granulomatous stage of rheumatic valvulitis is followed by organization and scar formation, a process that may be repeated with successive bouts of rheumatic activity The cusps become thickened, especially at the free edges, and more rigid. As the scar tissue shrinks, the cusps are retracted and their free edges rolled in. The result of these changes is defective coaptation of the cusps and regurgitation, the rigidity also produces obstruction. The neighboring edges of the cusps often become fused with resultant further stenosis, which becomes still more marked as the scar tissue shrinks. With the passage of years, secondary changes in the scarred valve, notably atheromatosis and calcification, may develop. Great masses of calcium salts may be deposited in the cusps and especially the valve ring, and constitute the most important anatomical substratum of many cases of aortic stenosis in middle life. The lumen may be reduced to minute dimensions; in this event, regurgitation is, of course, insignificant, even though the cusps are completely immobile

Investigations by Von Glahn and Pappenheimer[44] have shown that, in a high proportion of the cases, there are rheumatic lesions of the aorta of the same histological type as those in the valves and myocardium These may be so extensive as to lead to macroscopic changes in the aorta, I have known such a case to be mistaken for syphilitic aortitis at the postmortem table. Recent investigations have shown that not only the aorta and pulmonary artery (page 519) are implicated in the rheumatic state, but there may be widespread involvement of the vessels in different parts of the body.

With long-continued regurgitation, there often develops a thickening of the endocardium of the left ventricle in the vicinity of the aortic valve, especially along the interventricular septum. Often, there also form in this area crescentic thickenings of the endocardium or pocket-like formations with the concavity toward the aortic valve. The location and form of these changes indicate that the mechanical effects of the regurgitant stream are concerned in their production, but it is probable that these effects are exerted on an endocardium which is the site of chronic inflammation and therefore more apt to be distorted by the pressure.

The changes in the chambers of the heart resulting from aortic regurgitation are discussed below

Syphilitic Aortic Regurgitation —This valvular defect is a result of syphilitic aortitis, from which it evolves in the following fashion (for details, the reader is referred to the investigations of Martland[42] and of Saphir and Scott[43]):

The first lesions of syphilitic aortitis consist in obliterating arteritis with perivascular round-cell infiltration of the vasa vasorum in

the adventitia at the root of the aorta, a region in which these small vessels are especially numerous. The perivascular lesions extend into the media and the closure of the vessels leads to secondary nutritional changes in the media, the elastic tissue of which is extensively destroyed The resulting scar formation in the media produces the characteristic wrinkled and puckered appearance of the inner surface of the aorta. The lesions appear through the intima as white or gray patches, which become confluent The destruction of the medial elastic fibers results in diminution in the elasticity of the aorta, which is generally diffusely dilated, actual aneurysm developed in 16 of Saphir and Scott's 107 cases of syphilitic aortitis Syphilitic changes are usually best marked in the first part of the aorta, from a short distance above the aortic ring to the origin of the great vessels The remainder of the thoracic aorta may also be involved, but extensive implication of the abdominal aorta is rare The distribution of syphilis in the aorta is thus the reverse of that of arteriosclerosis, a difference that usually comes out clearly in the roentgen pictures. However, in elderly subjects syphilitic aortitis is frequently complicated by atherosclerosis of the aorta; atheroma, atheromatous ulcers, and calcification are to be attributed to the latter and not to lues

The syphilitic process extends from the aorta to the aortic valve *via* the commissures between the cusps White or gray, flat, elevated patches extend between the cusps, the lateral margins of which next become implicated The result is a widening of the commissures (up to 1 cm., Martland), which is regarded by Saphir and Scott and Martland as the earliest and macroscopically most characteristic evidence of syphilitic disease of the aortic valve It is also this separation of the aortic cusps which is responsible for the initiation of aortic regurgitation. In some cases, the commissural lesion is the only one found, but more often there is added thickening and rolling of the central portion of the free edge of the cusp with retraction, which of course accentuates the regurgitation greatly Dilatation of the aortic ring was also present in 26 of Saphir and Scott's 107 cases

Syphilitic disease of the aortic valve, as just described, produces regurgitation, but not stenosis of sufficient degree to impede the circulation.

A most important complication of syphilitic aortitis is narrowing or even complete obliteration of the mouths of the coronary arteries. This occurred in 33 per cent of Saphir and Scott's patients and was the cause of death in about 15 per cent of Martland's cases, most of the latter group showing little or no aortic regurgitation The syphilitic process rarely extends beyond the mouths of the coronaries changes along the mouths of the vessels being arteriosclerotic in nature Martland points out that the coronaries are especially

apt to be involved when they open anomalously into the aorta above the sinuses of Valsalva; the reason for this is that the sinuses are relatively spared by the syphilitic process. On rare occasions, syphilitic narrowing of the coronary ostia leads to myocardial infarction even though dissection of the coronary trunks reveals little change

Syphilitic Myocarditis.—The question of the frequency of specific syphilitic disease of the myocardium—syphilitic myocarditis—and of its significance in the production of heart failure and sudden death was brought to the fore by the extensive studies of Warthin.[57] Prior to his work, specific implication of the myocardium in acquired syphilis was considered a rarity and recognizable only by the presence of gummata or specific syphilitic granulation tissue in the myocardium. Warthin claimed, however, that by the use of appropriate staining methods he could demonstrate the presence of the Spirochæta pallida in numerous cases of heart failure and individuals who died suddenly without being aware that they had cardiac disease Warthin stated that the spirochetes lead to progressive fibrosis of the heart muscle with dilatation and hypertrophy, but that they may also be found in large numbers without surrounding reaction. However, subsequent investigators have almost invariably failed to confirm Warthin's findings and interpretations. There is no evidence that the histological changes described by Warthin are of specific syphilitic causation; most of them are probably due to ischemia resulting from the narrowing of the coronary mouths by syphilitic aortitis or from arteriosclerosis along the course of the coronary vessels Nor have other investigators using Warthin's and other technics found spirochetes in the heart muscle in other than congenital lues, and it seems possible that he was deceived by artefacts The subject is covered in detail in the review of Saphir,[48] who shows photographs of such artefacts It would thus seem that there is no evidence justifying the incrimination of specific syphilitic myocarditis as a cause of heart failure in syphilitic aortitis.

Arteriosclerotic Aortic Regurgitation.—Extensive arteriosclerosis of the aorta is almost always accompanied by arteriosclerotic lesions of the aortic valve. There are atheromatous changes in the cusps, predominantly on the side facing the sinuses of Valsalva, and often also fibrotic thickening of the valve ring and the cusps. Calcareous deposition in the ring and the base of the cusps is also frequent. Not uncommonly, arteriosclerotic dilatation of the aorta is accompanied by dilatation of the aortic ring (so-called Hodgson's disease) These lesions may result in a diastolic murmur, but rarely, if ever, in dynamically significant regurgitation. On the basis of protracted studies, Anitschkow[1] has concluded that: "Pure atherosclerosis . . . leads neither to the development of cicatricial tissue, nor deformation and ulceration of the valves and, therefore, has no great independent importance in the origin of cardiac valvular defects," and that "the so-called atherosclerotic defects of the heart valves have as their basis only the atheromatous transformation of the cicatricial tissue of the valves left as a result of endocarditis." Such atheromatous and calcific changes in valves which are the

seat of old rheumatic disease are very common; it would appear that this is the pathogenesis of most cases of calcific aortic stenosis (page 481).

Pathological Physiology.—**The Volume of Reflux.**—The aortic leak may be so small that the resulting alterations in the circulation are insignificant; the valvular defect can then be detected only by the diastolic murmur, which may be loud despite minimal insufficiency. All gradations occur between such small leaks and those in which regurgitation is almost as free as if the aortic valve were absent. Under these circumstances, the dynamics of the circulation are profoundly altered, an alteration which is spectacularly manifested by the Corrigan pulse and its accompaniments.

On the basis of experimental investigations by Stewart[54] and Wiggers,[58] it was widely accepted for a time that even in cases with the typical Corrigan pulse, the volume of reflux during each diastole is small—of the order of 10 per cent or less of the systolic output However, studies by MacCallum[39] and others showed that the regurgitation may be much greater The more recent careful experiments of Wiggers[59] reveal an average diastolic reflux of about 36 per cent of the systolic discharge, and the regurgitation may exceed 50 per cent. Since the aortic defects encountered in human necropsies are often quite as large as those produced experimentally, there is every reason to believe that the volume of reflux in clinical aortitic disease is of the same order as in these animal experiments. In free regurgitation, the reflux is readily visualized in the fluoroscope, for the excursions of the borders of the left ventricle are preternaturally great. Wiggers and Maltby[60] found that while the regurgitation in small leaks is well distributed through diastole, with large defects the reflex occurs almost entirely early in diastole, 68 per cent of the regurgitating blood re-entering the ventricle before the opening of the auriculo-ventricular valves.

The Effect of Aortic Regurgitation on the Heart.—The work of the left ventricle is approximately the product of its systolic discharge and the average pressure in the aorta during the period of ejection. In aortic regurgitation, the systolic discharge is increased by the volume of reflux, which we have just seen may be very great. The average pressure in the aorta is usually little changed, for the low minimal pressure is almost or quite counterbalanced by elevation in maximal pressure. *A priori*, therefore, one would anticipate that the work of the left ventricle is increased by an aortic leak. This expectation is confirmed by the occurrence of dilatation and hypertrophy of the left ventricle in both experimental and clinical aortic regurgitation in the absence of evidence of disease of the myocardium.

The development of dilatation and hypertrophy in aortic regurgitation has been studied experimentally on many occasions since Rosenbach[48] damaged the aortic valve and followed the evolution

of cardiac hypertrophy. All observers are agreed that, following the production of an aortic leak, the left ventricle gradually hypertrophies In the dog, Stewart[54] observed hypertrophy within a week of the injury to the aortic cusps, although Herrmann[22] could not demonstrate it in less than nineteen days. In Herrmann's dogs, the hypertrophy reached a maximum in an average of one hundred and ten days

Theoretically, one would anticipate dilatation of the left ventricle quickly after the production of experimental aortic incompetence. However, attempts to demonstrate this by roentgenographic observation have encountered some difficulty. One of the causes of this difficulty is an acceleration in rate, which was found by *Bazett and Sands*[4] *in most of their animals, and which must tend* to diminish the size of the cardiac silhouette. Bazett and Sands found that the heart shadow of most of their animals was decreased in size during the first week after the production of aortic regurgitation. On the other hand, Eyster, Meek and Hodges[13] were able to demonstrate an initial stage of cardiac dilatation in most of their dogs with aortic incompetence. They found that during this stage of dilatation preceding the development of hypertrophy, the functional capacity of the heart is diminished. Romberg and Hasenfeld[45] had previously found that after hypertrophy develops, the functional capacity of the heart is approximately normal, demonstrating the compensatory function of the hypertrophy.

In clinical aortic regurgitation, the degree of dilatation and hypertrophy varies widely, being governed not only by the size and duration of the leak, but doubtless also by the age of the individual, the state of the myocardium, the presence of other valvular lesions, and other factors Even with well-marked regurgitation, as demonstrated by the Corrigan pulse, fluoroscopic examination may reveal little enlargement of the heart; the transverse diameter is within normal limits and the enlargement is revealed only by downward elongation of the left ventricle. Should the patient succumb during this stage of practically perfect compensation—as *a result of intercurrent disease, subacute bacterial endocarditis, etc.* —the dilatation and hypertrophy may be confined almost entirely to the outflow tract of the left ventricle, the inflow tract being little affected, and the other chambers neither hypertrophied nor dilated. Such relatively slight hypertrophy and dilatation may be found even though the aortic leak is known to have been present for years. In these cases it is to be presumed that despite the increased diastolic filling of the left ventricle—which is filled from both the left auricle and the aorta—the chamber must empty practically as well as in health by means of an increased diastolic-systolic excursion. Actually fluoroscopic observation reveals an increase in the amplitude of the *excursion of the border of the left ventricle.* Further

study is needed to prove that in such cases the volume of blood entering the left ventricle from the auricle is not cut down as a result of the competing filling of the ventricle from the aorta. But against this assumption are the facts that there is no evidence of pulmonary engorgement and that the capacity for exercise of such patients may be practically normal.

Regarding the mode of contraction of the left ventricle in aortic regurgitation, Katz and Feil[27] found that the period of isometric contraction is shortened, which they attributed to an increased rate of contraction as well as to the low diastolic pressure in the aorta. They also found that the ejection phase is lengthened, so that the duration of systole is about normal The long ejection phase harmonizes with the large stroke volume.

Sooner or later, in the vast majority of instances of aortic regurgitation, the left ventricle, and then the other chambers of the heart, becomes greatly enlarged as a result of dilatation and hypertrophy. This will be considered in the next sections

The Effects of Aortic Regurgitation on the Peripheral Circulation — These are more spectacular than those of any other valvular lesion in the compensated stage, and include the following

1. *The Corrigan Pulse and Large Pulse Pressure* —The characteristic Corrigan pulse of aortic regurgitation rises abruptly and amply, seeming to bound against the palpating finger with a jerk, features which have led to its other names of pulsus celer and water-hammer pulse. The fall of the pulse is likewise abrupt and deep, whence the term collapsing pulse. These characteristics of the radial pulse are accentuated when the wrist is held high in the air. Often, the abnormal emptiness of the radial and other large arteries is evident on palpation. The wide and rapid excursions of the pulse may be prominent in the small arteries, and lead to such phenomena as shaking of the head synchronous with the heart beat (sign of De Musset, after the great poet, who presented the phenomenon) or arterial pulsation of the uvula or liver.

Corresponding to the palpatory characteristics of the pulse is a large pulse pressure, due not only to low diastolic tension, but most often also to corresponding elevation in systolic pressure Indeed, the diastolic pressure may be so low that it cannot be estimated by the auscultatory method, a clear sound being heard when the cuff is deflated. Exceptionally, the systolic pressure exceeds 200 mm. of mercury. The wide excursions of the blood pressure increase the wear and tear on the arteries, which become prematurely sclerotic and tortuous; they may also present well-marked muscular hypertrophy of the media Fluoroscopic examination often reveals dilatation and increased amplitude of pulsation of the aorta. For a considerable period, the dilatation is merely

"dynamic," the result of the larger volume of blood thrown into the aorta with each systole, and is then not evident at necropsy.

The prime cause of the low diastolic pressure is regurgitation into the left ventricle, which we have seen may exceed 50 per cent of the sytolic output of the chamber. The peripheral vasodilatation present in many cases (page 470) may also participate in the depression of the diastolic pressure. The rise in systolic pressure is a manifestation of the compensatory reaction of the left ventricle, which discharges into the aorta with each systole a volume of blood equal to the stroke volume of the right ventricle plus the volume of blood regurgitated. The result is a correspondingly greater systolic distention of the large arteries with rise in systolic pressure. Moreover, the systolic filling of the arteries occurs with great rapidity, and thus produces the pulsus celer, because of the empty state of these vessels at the end of diastole.

The large pulse wave and pulse pressure result in certain well-known auscultatory findings—pistol-shot sound and systolic-diastolic murmur—over the large arteries. These signs need not be discussed here; they are merely accompaniments of the large pulse pressure, and have lost their former diagnostic significance since the introduction of the sphygmomanometer furnished a more reliable method of demonstrating large pulse pressure.

2. *Reversal of the Arterial Blood Stream in Diastole.*—By optical registration of the volume pulses, Hewlett and Van Zwaluwenberg[24] showed that in aortic regurgitation there may be a reversal during each cardiac cycle in the direction of blood flow in the arteries of the arm, with a diastolic back-flow toward the heart. When a diastolic murmur is audible over the arteries in aortic regurgitation (Duroziez's sign), it is evidently correlated with the mechanism inducing this back-flow, for Blumgart and Ernstene[7] found that it is accentuated by compression of the limb distal to the site of auscultation.

3 *The Capillary Pulse*—Alternate flushing and blanching of the skin with each cardiac cycle is often present in free aortic regurgitation. The capillary pulse may be elicited by pressing the distal edge of the finger nail or gently applying a glass slide to the lip, and observing the margin of the blanched part. Or it may become prominent when the lobe of the ear or the finger tip is transilluminated with a flashlight. Lewis[33] has shown that capillary pulsation is primarily a result of arteriolar dilatation, and can be elicited in healthy persons by any maneuver, such as warming, which dilates the arterioles. For this reason, Lewis points out, the phenomenon loses its significance when brought out by such devices as warming or rubbing the skin. In aortic regurgitation, the great oscillations in the filling of the arteries presumably abet arteriolar dilatation in the production of capillary pulsation. According to Boas,[6] clinical

"capillary" pulsation is due not so much to the alternation in the filling of the capillaries as to emptying and filling of the subpapillary arterioles and venules, which are the primary determinants of the color of the skin. In rare instances of aortic insufficiency, pulsation can be seen in the veins on the back of the hand

That arteriolar dilatation is present in all instances of aortic regurgitation is not proved. Many patients with aortic incompetence have a flushed and warm skin—they look "healthy"—and it is to be presumed that their arterioles are dilated. Lewis points out that it is especially where the skin is flushed that capillary pulsation is present. But there are also some individuals with aortic regurgitation, especially when due to syphilis, who are strikingly pale and in whom, despite high pulse pressure, capillary pulsation cannot be demonstrated without the above mentioned artifices, which render the phenomenon meaningless In these pale subjects, there seems to be no evidence of arteriolar dilatation; indeed, cutaneous vasoconstriction would seem more probable, a conception which is supported by the relatively cool skin. Lewis states that pallor in aortic regurgitation, long described by clinicians as typical, is due to subacute bacterial endocarditis or active rheumatic infection. But I have repeatedly seen such pallor—in striking contrast to the usual appearance of the patient with mitral stenosis—in the absence of these conditions or of anemia The pallor may accompany the onset of left ventricular failure, and is then probably a manifestation of constriction of the superficial vessels evoked by the small volume of circulation due to the leak.

The mechanism of arteriolar dilatation in aortic incompetence, when it is present, is not clear. Perhaps it is a reflex result of mechanical stimulation of the receptors in the carotid sinus and aorta by the large volume of blood thrown abruptly into the aorta with each systole. Whether the patient is flushed or pale would, according to this conception, depend on whether this factor or vasoconstriction evoked by heart failure is predominant.

4. *Elevation of the Systolic Pressure in the Lower Extremities* — Hill and Rowlands[25] found that in free aortic regurgitation the systolic pressure in the lower extremities is much higher than in the arms; the difference may exceed 100 mm. of mercury The phenomenon is known as Hill's sign. There is much less, or no, difference in the diastolic pressure in the upper and lower extremities. Hill's sign is an exaggeration of a physiological phenomenon, for the systolic pressure is often a little higher in the lower extremities than in the upper, and Huerthle's[26] direct measurements in the dog revealed a higher systolic tension in the femoral than in the branchial artery. The cause of the remarkable increment in the femoral systolic pressure in free aortic regurgitation has not been unequivocally elucidated Hill and Rowlands attributed it

to constriction of the arteries of the lower extremity to assure the blood supply to the brain. In a thoughtful study, Gladstone[18] has advanced a dynamic explanation of Hill's sign. He points out that since the arteries to the upper extremity leave the aorta at a right angle, the blood pressure measured in the upper extremity comprises only the lateral pressure in the aorta and does not include the velocity head in the aorta. On the other hand, the arteries to the lower extremities are more nearly direct continuations of the aorta, so that the femoral blood pressure comprises the lateral pressure plus a large part of the velocity head in the aorta. In aortic regurgitation, the systolic velocity of blood flow is greatly accelerated, with consequent increase in the velocity factor of the aortic blood pressure, which receives expression in the femoral but not in the brachial blood pressure

Compensation and Decompensation in Aortic Regurgitation.—Aortic leaks may be fully compensated for many years. This is especially apt to be the case when the aortic incompetence has resulted from a non-recurrent bout of *rheumatic fever* early in life, which has entailed little residual damage to the myocardium and left in its wake a regurgitation too small to be documented by notable increase in pulse pressure Notwithstanding the presence of a long diastolic murmur, such individuals may be capable of hard work or participation in athletics and live to a ripe old age. In the cases in which high pulse pressure testifies to voluminous regurgitation, compensation is rarely so faultless, but may nevertheless be compatible with a number of years of tolerable activity. Most often, decompensation is the result of recurrent or continued activity of the rheumatic infection (page 346). The damage to the myocardium by the infection is doubtless most often the principal cause of the heart failure. But the mechanical factor of progressive deformity of the aortic valve due to protracted or recurrent infection is also of significance, for the increasing regurgitation or superadded stenosis adds to the work of the left ventricle Of course, complicating valvular lesions may also be concerned in the genesis of the circulatory failure. In those cases of aortic insufficiency which survive to middle or old age, ultimate failure may not be attributable to reactivation of the rheumatic infection, but to the other and often obscure causes of failure of the hypertrophic heart (page 334).

When the leak is a manifestation of *syphilitic aortitis*, the period of compensation is usually much shorter, measured from the time the murmur is first noted, than in the above mentioned instances of aortic regurgitation due to a single attack of rheumatic fever. In 107 autopsy cases of syphilitic aortic insufficiency studied by Scott,[31] six years was the longest period of compensation. However, Scott observed another patient with syphilitic aortic insufficiency in whom the leak was present for at least eighteen years prior to

death I saw a man who had had compensated luetic regurgitation for more than ten years When a diastolic murmur indicates that aortic incompetence has complicated tabes dorsalis, symptoms of heart failure may not appear for many years, if at all, probably largely because of the enforced inactivity of the patient. In the heart failure of syphilitic aortitis, it is often difficult to evaluate the pathogenetic significance of the aortic leak and the narrowing of the mouths of the coronary arteries (page 465). The question of specific myocardial involvement with luetic myocarditis has been discussed on page 466.

In *arteriosclerotic aortic leaks,* the regurgitation is of little significance in the clinical picture, which is conditioned by the associated arteriosclerosis with or without hypertension.

When *acute bacterial endocarditis* causes aortic incompetence, the leak produces little or no derangement of the circulation.

Subacute bacterial endocarditis, as pointed out by Libman,[35] generally develops in well-compensated valvular lesions. Most often, the development of the vegetations has little effect on the dynamics of the circulation In other cases, the murmur becomes louder and an increase in pulse pressure indicates that the regurgitation is augmented, but Libman has shown that heart failure is rare until the terminal stages, if it occurs at all

Functional aortic regurgitation (page 404) apparently is not voluminous enough to affect significantly the dynamics of the circulation.

In the rare *traumatic aortic regurgitation* due to rupture or avulsion of one or more cusps, usually previously more or less diseased, there may be fulminant left ventricular failure with a fatal issue. Other cases remain well compensated for years, Balfour[3] mentions one of twenty years' duration.

Clinical Picture of Compensated Aortic Regurgitation.—In well-compensated aortic incompetence, as already mentioned, there may be little enlargement of the heart for years, or solely elongation of the left ventricle that can only be discerned fluoroscopically But there are also cases in which compensation is fairly good with considerable dilatation of the left ventricle, although this state of affairs rarely lasts more than two or three years The heart rate is most often normal, but is sometimes very labile with marked acceleration on slight exertion or excitement. This lability of the heart rate may not be accompanied by other evidences of heart failure, although there are often indications of vasomotor instability in the form of easily induced flushing, sweating, or faintness. The electrocardiogram shows left axis deviation. There may also be inversion of the *T* wave in the first lead, but this usually portends left ventricular failure in the not distant future (page 436). The circulation time and venous pressure are normal.

During this period of compensation in aortic incompetence,

subjective symptoms may be entirely absent and the patient is surprised when told he has a murmur.

On the other hand, there are also many cases of aortic regurgitation with little evidence of heart failure, dyspnea appearing only after considerable exertion, in whom symptoms are present which are correlated with the hypertrophy and forcible action of the left ventricle. Of these, perhaps the most common are consciousness of the heart's action, occurring even when the heart rate is normal, and throbbing in the head or neck, which is apt to be especially annoying when in bed.

Much more important is *cardiac pain.* While pain is much more frequent in the syphilitic cases, it is more common in rheumatic aortic regurgitation than in any other rheumatic valvular lesion

In syphilitic aortitis with or without aortic regurgitation, thoracic pain is often an initial symptom and may long dominate the clinical picture. In a general way, two varieties of pain are encountered in syphilitic aortitis:

(*a*) Retromanubrial pain, described as dull, aching, burning, or constrictive, with or without relation to exercise, paroxysmal or constant, without radiation or extending into the back. This retromanubrial pain is in some way connected with the aortitis *per se*, for it may occur in the absence of aortic regurgitation or narrowing of the orifices of the coronary arteries. The pathogenesis is not clear, it has been attributed, without proof, to implication of the nerves in the adventitia of the aorta in the periaortitis that is present in syphilitic aortitis. Pressure on surrounding structures by the dilated aorta may also be concerned.

(*b*) Precordial pain with characteristics and radiations identical with those of the angina pectoris of coronary arteriosclerosis. It would seem that, in many cases at least, such syphilitic angina pectoris is due to narrowing of the mouths of the coronary arteries by the aortitis, Scott states that narrowing of the coronary orifices is almost always found when pain is present in syphilitic aortitis. Not rarely, syphilitic aortitis is complicated in elderly persons by arteriosclerosis along the course of the coronary arteries. This may, of course, produce anginal pain. When coronary thrombosis occurs in syphilitic aortitis, it is probably due to such complicating arteriosclerosis. In other cases of syphilitic aortic regurgitation, precordial pain may be due to the mechanism discussed below in connection with the cardiac pain of rheumatic aortic leaks.

The cardiac pain of rheumatic aortic regurgitation ranges from a dull ache in the cardiac region to agonizing thoracic constriction with radiation down the left arm or both arms. All the varieties of discomfort and radiations of pain encountered in coronary arteriosclerosis also occur in aortic insufficiency. Fear of death may be present and the exciting factors that operate in coronary

arteriosclerosis may also bring on the paroxysm which is associated with an aortic leak. The pain may be accompanied by profuse sweating. It has seemed to me that severe anginal attacks are more apt to occur in those patients with aortic regurgitation who are pale than in those who are flushed. I have also the impression that major anginal attacks in aortic regurgitation are more apt to supervene when the sufferer is at rest than be induced by exertion or excitement. In fact, I recently saw a man, aged twenty-three years, with rheumatic aortic regurgitation who repeatedly obtained relief from attacks of angina pectoris by getting out of bed and walking. The same therapeutic agents that may help the pain of coronary arteriosclerosis may also alleviate that of aortic regurgitation; Lauder Brunton's[8] first triumph with amyl nitrite was in a patient with the angina of aortic incompetence. In most of the violent anginal seizures in aortic regurgitation, there is marked rise in the systolic pressure, according to Lewis,[37] the rise in arterial tension precedes the pain, while Schwartz[50] observed it concomitantly with the seizure. I have seen severe paroxysms with little change in blood pressure In the milder attacks, there is rarely considerable alteration in blood pressure. The heart is usually rapid. Pallor or flushing, sweating, dyspnea, and palpitation are frequent but not constant manifestations of the attack Exceptionally, there is evidence of left ventricular failure during a protracted attack in the form of moist râles at the bases, but Schwartz did not observe frank pulmonary edema in any of his 5 cases. Schwartz noted that severe anginal seizures in patients with aortic insufficiency tend to occur during a period of a year or less and then disappear, so that the patient may enjoy relatively good health for a number of years. However, I observed a girl with rheumatic aortic insufficiency who had extremely severe anginal attacks requiring morphine over a period of more than five years.

The pathogenesis of cardiac pain in rheumatic aortic insufficiency has been extensively discussed. The attacks may occur in the absence of well-marked rheumatic lesions of the aorta or narrowing of the coronary arteries (Keefer and Resnik,[29] own observations). The best founded theory would seem to be that of Keefer and Resnik, who attribute the pain to ischemia of the myocardium due to the low diastolic pressure. In all the instances of angina in aortic regurgitation that I have seen the diastolic pressure has been very low; usually, but not always, the systolic pressure has been abnormally high. While the question of the variations in coronary flow during the phases of the cardiac cycle is still *sub judice*, the work of Anrep[2] indicates that the average aortic pressure during diastole is one of the primary factors determining coronary flow. In animal experiments, Smith, Miller and Graber[52] showed that

following the production of aortic regurgitation, coronary flow is markedly curtailed (in one of their experiments from 240 to 150 cc. per minute) In experimental aortic regurgitation, Green[19] likewise found that coronary blood flow was diminished; the diminution occurred during diastole as a result of lowered aortic diastolic pressure, and was mitigated to a considerable extent by a concomitant increase in the coronary flow during systole due to the systolic peripheral coronary resistance being relatively low in comparison to aortic pressure Moreover, the blood flow to the myocardium may be hampered by coronary sclerosis remaining as a heritage from the original rheumatic infection (page 345); even though *the sclerosis does not narrow the coronaries, it may interfere* with the *increase* in blood flow necessary for the hypertrophied left ventricle performing so much work. In aortic regurgitation there is, therefore, the combination of increased demand for blood as a result of left ventricular hypertrophy and decreased coronary flow as a result of low diastolic pressure and perhaps sometimes coronary sclerosis. That anginal pain should frequently develop under these circumstances is not surprising in view of the strong evidence indicating that myocardial ischemia is the basic cause of such pain (page 414). *Entirely obscure is the immediate precipitating mechanism* of the paroxysm, and especially why the anginal pain of aortic regurgitation is so apt to appear at rest and is sometimes relieved by moving about.

Some patients with aortic regurgitation *suffer from attacks of vertigo* and even brief *syncope,* presumably due to transitory cerebral ischemia, although there are no other evidences of heart failure. However, in my experience such cerebral symptoms have been rare when the patient was otherwise well compensated.

Left Ventricular Failure in Aortic Regurgitation.—Heart failure in aortic regurgitation is almost always initiated as isolated left ventricular failure. The first symptom is usually dyspnea. While the initial dyspnea is most often exertional, a nocturnal paroxysm of cardiac asthma ushers in circulatory failure in a higher proportion of cases of aortic incompetence than of other valvular lesions. As pointed out by Longcope,[27] paroxysmal dyspnea is especially frequent in syphilitic aortitis Keefer and Resnik[28] found that paroxysmal dyspnea occurs in syphilitic aortitis only when the latter is associated with aortic incompetence, hypertension or aneurysm; according to their investigations, syphilitic aortitis *per se* does not occasion cardiac asthma. But I have seen cases in which syphilitic narrowing of the mouths of the coronaries seemed the most likely cause of severe paroxysmal dyspnea. Cardiac asthma may be the only symptom of syphilitic aortic insufficiency for months (Longcope[27]), so that the cases are sometimes confused with bronchial asthma. However, cardiac asthma is not characteristic of syphilitic

aortic regurgitation; it also occurs with leaks of rheumatic or arteriosclerotic etiology.

The dyspnea is generally associated with orthopnea and may attain agonizing severity; for days at a time, the victim may sit in a chair or with his legs hanging over the side of the bed. Frequently in the syphilitic cases, much less often when the leak is due to rheumatic fever, the tribulations of the sufferer are increased by precordial or retrosternal pains The pains have been described in the section on the compensated stage because they are not consequences of heart failure, and may long precede its inception Of all valvular lesions, syphilitic aortic insufficiency is the one most apt to be associated with excruciating suffering. The suffering is usually more intense during the period of isolated left ventricular failure than in the later stages when the heart gives way, then the dyspnea and orthopnea are most often ameliorated, presumably as a result of diminution in pulmonary engorgement, and the anginal pains often disappear

There may be other symptoms of pulmonary engorgement during the stage of isolated left ventricular failure Of these, cough, with or without expectoration, is the most common. There may be blood-streaked sputum or even copious hemoptysis. These symptoms may be due either to the pulmonary or bronchial engorgement manifesting the left ventricular failure or, in syphilitic aortitis and rarely in arteriosclerotic dilatation of the aorta, they may result from pressure on a bronchus by the dilated aorta Occasionally, massive pulmonary edema develops and may prove fatal

Vertigo is not uncommon, and syncope occurs in rare cases. These symptoms are presumably due to transitory cerebral anemia.

Objectively, cyanosis is rarely deep and, in contrast to the usual state of affairs in mitral disease, may be completely absent despite severe dyspnea Pallor is often the dominant characteristic of the skin, but there are patients who remain flushed even when severely decompensated The physical evidences of hypertrophy and dilatation of the left ventricle are present. At first, during the stage when the dilatation involves mostly the outflow tract (page 298), the enlargement is more downward than to the left, but later the transverse diameter becomes very large The most capacious left ventricle encountered by the physician is in aortic regurgitation with decompensation of long standing Despite the absence of venous stasis, the other chambers may also be hypertrophied and dilated, but proportionately less than the left ventricle; only exceptionally does a case of aortic regurgitation come to necropsy during the period when the enlargement is confined to the left ventricle. The heart rate is more or less accelerated While there may be premature contractions, auricular fibrillation is very rare during the stage of isolated left ventricular failure. The aortic diastolic mur-

mur often becomes fainter as the heart falls; it may not be distinguishable when the rate is rapid, again to become obvious when the heart slows. Gallop rhythm is common. Accentuation of the pulmonic second sound often testifies to the hypertension of the lesser circulation. The Flint murmur may be present.

The Flint Murmur.—Austin Flint[15] described the occurrence of a rumbling presystolic murmur at the mitral area in patients with aortic regurgitation, although the murmur simulated that of mitral stenosis, the absence of organic stenosis was proved at necropsy. Thayer[35] observed a Flint murmur at some time in the clinical course of 33 of 74 cases of aortic incompetence in which mitral stenosis was absent at necropsy. This is a much higher incidence of the Flint murmur than I have encountered, and is probably due to the fact that Thayer considered only hospital cases which came to necropsy. Laubry and Pezzi[31] have pointed out that the Flint murmur is not present in well-compensated aortic regurgitation; when it is heard, there are evidences of left ventricular failure Further, as pointed out by Laubry and Pezzi and as I have repeatedly observed, the Flint murmur may disappear as the heart improves with digitalization The Flint murmur would thus appear to be one of the manifestations of left ventricular failure, which is the reason why it is discussed at this point.

Apart from the cases in which the murmur disappears with the improvement of the heart, the diagnosis of a Flint murmur can hardly be made with any assurance in rheumatic aortic regurgitation, for it may simulate the murmur of mitral stenosis in all respects, be accompanied by a thrill, and even be followed by a snappy first sound (30 per cent of Thayer's cases) But in syphilitic aortic incompetence, the appearance of a vibratory presystolic murmur at the apex is almost always due to the aortic defect and not to organic mitral stenosis.

The pathogenesis of the Flint murmur has been much disputed. Flint believed that the regurgitant stream from the aorta floats the mitral curtains into apposition, so that they are set into vibration by the direct current produced by auricular systole. A much more plausible explanation is that of Guitéras,[21] who suggested that the regurgitant stream strikes the anterior flap of the mitral valve and drives it into such a position that it is set in vibration by the auriculo-systolic blood current. Struck by the fact that the Flint murmur is encountered when heart failure is present, Laubry and Pezzi maintain and bring graphic evidence in favor of the view that the Flint murmur is a presystolic gallop rhythm engrafted on the diastolic murmur, and simulating to the ear a presystolic murmur. To me, the explanation of Guitéras seems the most plausible. The fact that the Flint murmur develops in the presence of left ventricular failure is perhaps explained as follows· When the left ventricle weakens and does not empty completely, auricular systole is more powerful and thus more apt to set the anterior flap of the mitral valve, pushed up by the regurgitant stream, into audible vibration According to the observations of Herrmann,[23] a Flint murmur is especially apt to develop if the posterior cusps of the aortic valve are incompetent.

Very often, the characteristic Corrigan pulse becomes less distinct as the left ventricle fails; this is probably due to diminution in the systolic discharge of the left ventricle, and perhaps also to an impediment to regurgitation by the elevation in diastolic intraventricular tension that marks the failure of the left ventricle. The evidences of systemic venous engorgement are absent during the

stage of isolated left ventricular failure and the venous pressure is normal.

The manifestations of pulmonary engorgement are the classical ones described in Chapter XIII.

Systemic Venous Engorgement in Aortic Regurgitation.—If the patient does not succumb during the stage of isolated left ventricular failure, venous engorgement sooner or later develops. The cervical veins and liver swell, hydrothorax and less often ascites appear, and the venous pressure rises Fibrillation of the auricles may set in but is exceptional in aortic valvular defects; Cowan and Ritchie[11] encountered it only 12 times in 300 cases of aortic incompetence We have already mentioned that *pari passu* with the development of systemic venous engorgement the dyspnea and especially the orthopnea may be ameliorated. There is every reason to believe that the pathogenesis of systemic venous engorgement in aortic regurgitation is similar to that in hypertension, to the discussion of which the reader is referred (page 446). It may be remarked that exquisite examples of obturation of the right ventricle by a bulging interventricular septum are not uncommonly encountered at the necropsy of individuals with aortic regurgitation and systemic venous engorgement.

Course of Heart Failure in Aortic Regurgitation.—The stage of isolated left ventricular failure may last from a short period to a number of years. Many persons with rheumatic aortic insufficiency are short of breath on moderate exertion but otherwise able to pursue their usual way of life for a number of years, even a decade or more. This is less often true in syphilitic aortic regurgitation Rheumatic patients often improve enough to be up and about from several episodes of decompensation marked by severe left ventricular failure, or even from such with systemic venous engorgegorgement. This, again, is much less common in the syphilitic cases In a general way, the prognosis of the syphilitic cases is decidedly worse than those of rheumatic etiology, whether they are seen when still well compensated or after heart failure has set in This is probably largely due to differences in the nature of the infection. Once syphilis has persisted for enough years to produce aortitis, eradication of the infection is unlikely, although recent work (page 786) shows that adequate treatment improves the prognosis On the other hand, rheumatic infection often becomes quiescent, and may even subside completely after having produced regurgitation; we have seen that a major proportion of episodes of decompensation in rheumatic valvular disease are direct consequences of the activity of the rheumatic infection. Moreover, the prognosis in syphilitic aortic insufficiency is also clouded by the location of the aortitis with its great tendency to narrow the orifices of the coronary arteries.

It is an old clinical experience that once decompensation occurs in aortic insufficiency, the outlook is usually not as good as in the cardiac failure of mitral disease. One of the reasons for this difference is that a considerable proportion of the aortic cases are syphilitic Moreover, heart failure in mitral disease is more often precipitated by auricular fibrillation, which is so frequently amenable to digitalization

Individuals with aortic insufficiency have a marked predisposition to *sudden death*, either when seemingly well compensated—they may not have known of heart disease—or after chronic failure has set in. Martland[42] found that 101 of 300 instances of sudden death were due to syphilitic aortitis, and in 36 of these aortic regurgitation was the predominant lesion. The predisposition to sudden death is perhaps largely correlated with the great hypertrophy of the left ventricle and the low diastolic pressure, as a result of which the factor of safety of the blood supply to the heart is less than in healthy persons In the syphilitic cases, which are the more liable to sudden death, the narrowing of the mouths of the coronary arteries is doubtless often significant.

Simulation of Heart Failure in Syphilitic Aortitis.—In syphilitic aortitis with or without aortic insufficiency, and much less often in arteriosclerotic dilatation of the aorta, symptoms due to the dilatation of the aorta may simulate heart failure. Pressure of the dilated aorta on the main bronchi may produce continuous or paroxysmal dyspnea, cough, and exceptionally bloody expectoration, symptoms which in the presence of aortic insufficiency may be misinterpreted as due to left ventricular failure. Differentiation between such pressure symptoms and left ventricular failure is often facilitated by measurement of the circulation time (page 55), which is normal in compression and almost invariably prolonged in left ventricular failure severe enough to produce symptoms. Occasionally, compression of the superior vena cava by the dilated aorta (or rarely by syphilitic periaortitis and mediastinitis) leads to swelling of the cervical veins and high pressure in the veins of the upper extremities, thus simulating right ventricular failure. But the picture is differentiated from insufficiency of the right side of the heart by the absence of swelling of the liver or other venous engorgement below the diaphragm From the point of view of therapy, it is most important that symptoms due to heart failure be differentiated from those of compression by a dilated aorta.

AORTIC STENOSIS

As a rule, aortic stenosis is merely one element in rheumatic heart disease. It may be accompanied by aortic regurgitation, mitral defect, and myocardial and pericardial disease. In the

pathogenesis of heart failure in such cases, aortic stenosis most often plays only a subordinate rôle. Actually, as a previously leaky valve narrows, the added work thrown on the left ventricle by the stenosis may no more than substitute for that spared the chamber by the diminution in regurgitation due to the constriction of the aortic aperture.

In another group of cases, the clinical picture is due predominantly or solely to aortic stenosis The majority of these patients are past fifty years of age when symptoms of cardiac disease appear, although the history or necropsy findings may show that marked aortic stenosis has been present for many years. A large proportion of these individuals (Margolies[41] *et al.*) never develop cardiac symptoms and succumb to an independent disease Aortic stenosis is not rarely a surprise at necropsy Contrary to other valvular lesions, and for reasons which have not been elucidated, males are much more often affected than females Although the anatomical findings render it hardly likely that the valve shuts faultlessly, aortic regurgitation is usually insignificant and often cannot be demonstrated during life. In the large majority of instances, massive calcification of the stenotic aortic valve is found at necropsy, and can sometimes be demonstrated roentgenologically during life. Large calcareous deposits are located in the ring and especially in the basal portion of the scarred and deformed cusps The masses often project into the sinuses of Valsalva, which may be almost filled up Extensive atheromatous change is generally also present The other valves show little or no change

While such calcific aortic stenosis in the middle aged and elderly was formerly regarded as primarily arteriosclerotic in origin, it seems that at least most often the lesion is due to rheumatic fever, a history of this infection was definite in 11 of Christian's[10] 21 cases and probable in 2 of the others Dry and Willius[12] also regard calcareous aortic stenosis as of rheumatic origin Presumably, in view of the frequent paucity or absence of evidence of old rheumatic changes in the other valves, myocardium, and pericardium, the aortic cusps bore the brunt of the original infection, which healed and left behind only the deformity of the aortic valve. Such a solitary defect of the aortic valve is readily compensated by hypertrophy of the left ventricle and the patient has no symptoms of heart disease for a long time But in the course of years shrinkage of the scarred and fused aortic cusps with secondary degenerative changes, including calcification, further narrows the aortic aperture, and the functional capacity of the hypertrophic left ventricle decreases with advancing age, so that symptoms of heart failure finally make their appearance. The histological observation of Sohval and Gross[53] convinced them that, in addition to the rheumatic cases, there are also many instances of non-rheumatic calcific aortic stenosis Libman[35] has suggested that some of the cases may occur on the basis of a congenital bicuspid valve, and Libman and Cabot[9] believe that some may be the outcome of healed bacterial endocarditis

Syphilis is not concerned in the etiology of aortic stenosis, the complication of syphilitic aortitis by aortic regurgitation is due primarily to

widening of the commissure between the cusps, a process which does not lead to aortic stenosis (page 465). Likewise, arteriosclerosis *per se* rarely, if ever, produces the fusion of the aortic cusps which is generally the main element in aortic stenosis On rare occasions, the vegetations of bacterial endocarditis produce marked stenosis of the aortic opening.

Compensated Aortic Stenosis.—In the light of Starling's law of the heart, the process of compensation in aortic stenosis would seem to be as follows: Constriction of the aortic orifice augments the resistance to the systole of the left ventricle. In consequence, *the chamber does not empty as completely as before.* And if an unchanged volume of blood enters the left ventricle from the auricle during the succeeding ventricular diastole, the diastolic filling is greater. According to Starling's law, the strength of the following systole is increased and the left ventricle, despite the greater resistance to be overcome, discharges the same volume of blood as before the narrowing of the aortic orifice. Circulatory equilibrium has been restored, although only at the expense of greater diastolic and systolic blood content of the left ventricle, *i. e.*, of dilatation. But we have *seen that this is the condition which leads to the development* of hypertrophy of the left ventricle (page 310), and this gradually appears. The hypertrophy of the left ventricle increases the absolute strength of its systole, so that, starting from a normal diastolic filling, it is able to overcome the increased resistance due to the stenosis, *i. e.*, hypertrophy has substituted for dilatation When this takes place, the dynamics of the circulation have been restored to normal except that the systolic pressure within the left ventricle is elevated. Further, Katz and Feil[27] have shown that in aortic stenosis both the isometric contraction period and the ejection phase are prolonged, they point out that the prolongation of the ejection time tends to compensate for a reduced rate of ejection.

In human aortic stenosis of the type described in the preceding paragraphs, the narrowing of the orifice develops very slowly, most often over a period of years. Consequently, time is afforded for hypertrophy to substitute for dilatation at each stage of the process. In most cases of well compensated aortic stenosis, radiographic examination reveals little, if any, enlargement of the cardiac silhouette; there is only evidence of left ventricular hypertrophy (page 362). And if such a patient succumbs to an independent cause, which is not rare, the necropsy discloses the left ventricle to be markedly hypertrophied but not dilated. Aortic stenosis furnishes the classical examples of "concentric" hypertrophy, *i. e.*, hypertrophy without notable dilatation, in which postmortem contraction of the thickened myocardium causes the cavity to appear smaller than usual. The myocardium of the left ventricle may exceed 25 mm. in thickness, and the papillary muscles and trabeculæ are massive and rounded. In individuals who succumb during

perfect compensation from independent causes, the other chambers may be normal

During the stage of faultless compensation, aortic stenosis often produces few or no subjective symptoms, and is generally discovered while the subject is being examined for insurance or another condition. There may be consciousness of the heart's action, even though it is not rapid, or a dull ache in the cardiac region. Classical angina pectoris was present in 4 of Boas'[5] 19 patients with aortic stenosis; some of the attacks simulated coronary thrombosis. McGinn and White[38] encountered angina in 19 per cent of their cases of aortic stenosis. In 2 cases with angina which came to necropsy, Boas found the coronary arteries unobstructed. The angina is plausibly explained on the basis of myocardial ischemia, for the hypertrophy results in an increased muscle mass and Green[19] has shown that in experimental aortic stenosis in the dog coronary blood flow is diminished. The diminished coronary flow is probably due to the small cardiac output and perhaps also, as indicated by the experimental findings of Green, to an increase in the systolic coronary resistance resulting from the systolic pressure within the left ventricle being so much higher than the aortic pressure. Corroboration of the conception that the angina of aortic stenosis (like all other angina) is due to myocardial ischemia is afforded by the electrocardiographic findings and Friedberg and Sohval's[16] finding of fresh myomalacia in the absence of coronary occlusion In other and perhaps more frequent cases, coronary arteriosclerosis is concerned in the causation of the angina. Vertigo and faintness are occasional complaints; actual syncope is a rarity during the stage of compensation

The physical findings emanating directly from the deformed cusps—thrill, murmur and weakness of the aortic second sound—will not be described here; for a discussion of their occurrence and interpretation, the reader is referred to the paper of McGinn and White.[38] The diastolic murmur of aortic regurgitation may or may not be audible. Often, the hypertrophy of the left ventricle is revealed by a heaving apex beat, but this may be concealed by emphysema. As already mentioned, neither physical nor radiographic examination may show the silhouette of the heart to be increased above the upper limit of the normal, usually, the rounding of the left ventricular border due to hypertrophy is evident on fluoroscopy. On the other hand, there are also cases in which, despite the absence of dyspnea or other symptoms of heart failure, the left ventricle is considerably enlarged, especially downward but also to the left. There can be no doubt that considerable dilatation of the left ventricle is present in such instances, but for the time being notable engorgement of the lungs is averted by the increased force of left ventricular systole due to the dilatation and hyper-

trophy. Such a state of tolerable compensation despite dilatation of the left ventricle may continue for years. The first sound at the apex is often booming and seems prolonged. The heart rate is usually within normal limits. Exceptionally, in the absence of conduction disturbances the heart is slowed to between 50 and 60 beats per minute, whether the slow rates occur in the cases with the marked prolongation of systole described by Katz and Feil (page 482) has not been studied. Boas and others have pointed out that aortic stenosis is occasionally complicated by auriculo-ventricular or bundle-branch block Anatomical investigations have shown that the heart block may be due to the extension of the calcifying process from the aortic ring into the interventricular septum with implication of the bundle of His (Uehlinger[56]). However, the findings of Friedberg and Sohval[16] indicate that heart block in aortic stenosis is not always due to such gross organic implication of the bundle, Boas and they point out that the conduction disturbance may be transient and sometimes, like the angina, occur only on exertion.

The *electrocardiogram* usually shows rotation of the electrical axis to the left and quite high voltage As in all varieties of left ventricular strain, the *T* wave may be inverted in the first lead. Of special interest is the fact that aortic stenosis may result in elevation of the *RS–T* interval in the first and second leads simulating the findings in coronary thrombosis (*cf* Master, Jaffe and Dack[40]) This elevation of the *RS–T* interval is doubtless an expression of myocardial ischemia. In accord with this explanation, Friedberg and Sohval found fresh myomalacia in several instances of aortic stenosis without coronary occlusion

Calcification of the aortic valve can often be detected *fluoroscopically* or on the film

In some instances of aortic stenosis, the *pulse* is rather characteristic It is small and, what is most significant, rises gradually to a summit, which may be prolonged as a plateau. The slow rise is the direct expression of the small orifice through which the left ventricle ejects its blood Libman[34] has pointed out that the contrast between the heaving apex beat and the absence of retromanubrial pulsation is sometimes of aid in the recognition of aortic stenosis. Tracings show that an additional wave may be present on the upstroke of the pulse, but only rarely is such an *anacrotic pulse* sufficiently pronounced to be detected by unaided palpation On rare occasions, the anacrotism is so ample as to give the impression of a double apex to the sphygmogram; even more rarely the double beat (pulsus bisferiens) can be detected by palpation. The origin of the anacrotic pulse is not clear. Feil and Katz's[14] optical records indicate that the anacrotic wave is the peripheral manifestation of a change from rapid to slower ejection by the left ventricle.

but the mechanism which causes this is obscure. The anacrotic pulse is also occasionally observed in aneurysm of the aorta, compression of the artery by a tumor central to the site of compression, severe arteriosclerosis, and other conditions; it can be produced in the sphygmogram of the healthy person by increasing the pressure of the instrument against the vessel. Another change in the pulse which has been observed in aortic stenosis is delay (pulsus tardus), instead of the normal interval of 0.7 to 0 1 second between the apex beat and the radial pulse, this may be increased to 0.2 second (Mouquin[43]). The delay is sometimes appreciable by simultaneous palpation, or better auscultation and palpation, of the apex and the pulse

While these changes in the pulse are evident in some instances of aortic stenosis, in others they are not appreciable to simple palpation The latter often reveals nothing characteristic in aortic stenosis severe enough to lead to heart failure and which is found at necropsy to be very tight. Tracings would doubtless bring out the slow rise of the pulse more often, but they are rarely made nowadays.

The *arterial pressure* is most often normal despite tight aortic stenosis. This is not surprising, for Roy and Adami[47] showed long ago that the ascending aorta of the dog can be greatly constricted by a clamp without causing significant fall of pressure in the carotids As experiments show, more forceful contraction of the left ventricle maintains the stroke volume despite very marked stenosis And even when the left ventricle fails, vasoconstriction militates against fall in blood pressure In rather exceptional cases of aortic stenosis, the systolic and pulse pressures are depressed This is probably due to the prolongation of systolic discharge; since the arteries continue to empty at their usual rate, the maximum blood content, and consequently the systolic pressure, are not as high as they would be in the absence of stenosis In middle-aged and elderly individuals with aortic stenosis, essential hypertension is a not uncommon association, but of course the elevation of blood pressure is not directly correlated with the valvular lesion When, as is often the case, aortic regurgitation and stenosis are both present, the stenosis tends to diminish both the fall in diastolic pressure and the rise in systolic pressure due to the regurgitation

The duration of the stage of compensation in aortic stenosis when associated with little or no aortic regurgitation and uncomplicated by other valvular lesions is often remarkably long Especially when the lesion is first detected in middle life, the individual may remain capable of hard work for one or even two decades As already mentioned, death is often due to an independent cause When there is also well-marked regurgitation, the prognosis is not so good, but some of these patients also do well for years

Heart Failure in Aortic Stenosis.—This is initiated as left ventricular failure. Most often, the initial symptom is dyspnea on exertion. Less commonly, heart failure is ushered in brusquely by an attack of cardiac asthma. Palpitation and precordial pain are other frequent early symptoms, which may have also been present during the compensated stage and are sometimes correlated with complicating coronary arteriosclerosis. The latter may result in severe angina. The pulmonary engorgement is often manifested by cough, which in these elderly patients may be mistakenly attributed to "bronchitis." Bloody expectoration is not uncommon, and frank hemoptysis is an occasional event. As in all forms of heart failure in the elderly, insomnia and weakness are common complaints. Much less frequent (22 per cent of McGinn and White's patients) but sometimes striking, are such manifestations of cerebral ischemia as vertigo, faintness and syncope; the advanced age and cerbral arteriosclerosis of most of the patients perhaps abet the small cardiac output in the causation of these symptoms. Gallavardin[17] and others have pointed out that vertigo and syncope in aortic stenosis are sometimes precipitated by exertion. Since tight stenosis prevents notable increase in cardiac output, the deviation of more blood to the extremities during exercise may readily entail cerebral ischemia and thus produce the dizziness and fainting.

The duration of the stage of isolated left ventricular failure is variable. Some of the patients continue to complain only of dyspnea on exertion and perhaps precordial pain or dyspnea for years and are able to get about fairly well. Others have several admissions to the hospital during a few years because of exertional and paroxysmal dyspnea, recovering each time sufficiently to be fairly active. In a considerable proportion of the cases, however, once heart failure sets in, it is rapidly progressive. There is always danger of the usual complications of left ventricular failure—bronchopneumonia, pulmonary infarction, and acute edema of the lungs. The patient may succumb to any of these during the stage of left ventricular failure. Sudden death is not rare; sometimes, this occurs in individuals who were not aware of their cardiac lesion.

If the patient does not succumb during the stage of isolated left ventricular failure, evidences of systemic venous engorgement sooner or later make their appearance. These consist in the banal swelling of the cervical veins, enlargement of the liver, edema, serous effusions and rise in venous pressure. The pathogenesis of systemic venous engorgement in aortic stenosis is presumably similar to that in other forms of left ventricular failure (page 440). Once venous engorgement has appeared, the results of treatment are generally not so good as in hypertensive heart disease. However, in some cases the patients improve sufficiently to be up and about for a time.

Objective Findings.—Physical examination reveals the left ventricle to be enlarged downward and to the left. During the stage of isolated left ventricular failure, the enlargement may be confined almost entirely to the left ventricle. Later, all the chambers participate, but the enlargement of the left ventricle is predominant. The heart may become extremely large, but the average size is not as great as when regurgitation is the dominant defect. Even when there has been a long period of heart failure, the hypertrophy of the left ventricle is more marked in proportion to the dilatation than in aortic regurgitation. The heaving apex beat becomes more diffuse. The heart accelerates, but generally not as much as in predominant regurgitation It is not uncommon to encounter severe heart failure in aortic stenosis with a rate of between 80 and 90. The occurrence of very slow rates due to heart block has already been mentioned. Most often, apart from premature contractions, the rhythm remains regular; auricular fibrillation was present in only 2 of Christian's[10] 16 patients. Gallop rhythm is frequent. The harsh aortic murmur and thrill often become fainter as the heart fails. The systolic murmur of functional mitral insufficiency usually appears, so that if previous examination had not shown that the patient has only aortic stenosis, a multivalvular lesion may be diagnosed. Occasionally, alternation of the pulse develops. The evidences of pulmonary and systemic venous engorgement are the usual ones.

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CHAPTER XXVII

HEART FAILURE INITIATED BY INSUFFICIENCY OF THE LEFT SIDE OF THE HEART. IV. MITRAL VALVULAR LESIONS

Both incompetence and stenosis of the mitral valve strain the left side of the heart and thus predispose to cardiac insufficiency initiated as left-sided failure with pulmonary engorgement. In most instances of rheumatic heart disease, the mechanical consequences of these defects of the mitral valve constitute *one* of the factors in the pathogenesis of the heart failure that usually eventuates. Primary atherosclerotic changes develop in the mitral valve in hypertensive and arteriosclerotic heart disease, but they interfere with the function of the valve so little that the dynamic repercussions on the circulation are slight and their rôle in the production of heart failure almost always insignificant.

ANATOMICAL FINDINGS IN RHEUMATIC MITRAL REGURGITATION AND STENOSIS

These will be discussed together because by the time of necropsy both are generally present, although, as will be seen below, almost pure regurgitation occurs much more often than has been the usual opinion A brief description of the histological findings in rheumatic valvulitis has already been given in conjunction with aortic disease (page 463). The identical lesions occur in the mitral valve They are located not only in the curtains but also in the fibrous ring, chordæ tendinæ and neighboring parietal endocardium. In addition, the papillary muscles and myocardium surrounding the ring are implicated in the myocarditis which is practically always a component of rheumatic carditis.

The minute verrucæ which form especially along the closure lines of the *mitral flaps* as the most characteristic evidence of active rheumatic valvular disease can hardly be the cause of quantitatively important regurgitation, although they are perhaps concerned in the pathogenesis of the faint apical systolic murmur which so commonly appears early in rheumatic fever. It would seem probable, however, in view of the rheumatic myocarditis which is present at this time, that the functional factor of dilatation of the left ventricle is the principal cause of these early systolic murmurs and the presumably minimal regurgitation which they document.

Only at a later stage of rheumatic carditis does quantitatively significant regurgitation develop, and then it is due to deformity

of the valve produced by the organization of the inflammatory exudate terminating in cicatrization. Postmortem studies by Bland, White and Jones[8] indicate that such deformity does not begin to be significant until after the first year following infection The individual structures of the valve are affected as follows:

The *curtains* become irregularly thickened and more rigid, which interferes with their coaptation during ventricular systole and thus causes regurgitation. The regurgitation is accentuated by the shortening of the curtains, which often ultimately results from contraction of the scar tissue. The curtains may become so rigid that they are fixed in a position in which not only is closure incomplete with resulting regurgitation, but they offer considerable resistance to the auriculo-ventricular blood current and thus produce stenosis, this factor is especially important when the flaps are calcified However, the most important factor in the production of tight mitral stenosis is usually the fusion of the adjacent borders of the flaps starting at the base and progressing toward the central portions of the borders. This diminishes the circumference of the orifice, which becomes still smaller as the scar tissue in the fused curtains shrink. When the circumference is less than 7.5 cm. in an adult (normal, 8 to 11 cm. according to Dana and Reidy[10]), significant stenosis is present. Sometimes the process results in what appears from the auricular side as a diaphragm between the auricle and ventricle punctured only by a narrow, slit-like opening —the so-called button-hole form of mitral stenosis. In other cases, the fusion of the cusps with one another and with the chordæ tendinæ converts the mitral valve into an irregularly conical structure with the base toward the auricle and the apex toward the ventricle—the funnel form of mitral stenosis. According to Sansom,[11] the funnel-shaped variety is 8 times more common in children, while the button-hole variety is 25 times more frequent in adults. In extreme instances of mitral stenosis, the mitral orifice is reduced to a slit perhaps 1 cm. long and a few millimeters broad.

Changes in the *chordæ tendinæ* are often of great importance in the production of mitral valvular defects. The cords become shortened, thickened, fused together into thick masses, and adherent over wide areas to the ventricular surface of the flaps and the parietal endocardium. The process of fusion and adhesion generally starts and is most severe at the web-like insertions of the chordæ on the flaps. The shortening of the cords must be a potent factor in the production of regurgitation, and the cases are not uncommon in which the changes in the cords seem to be much more important in the causation of mitral regurgitation than the alteration of the flaps. The fusion of the cords with one another and the flaps is a significant factor in the production of the funnel form

of mitral stenosis. The papillary muscles are often fibrotic in mitral disease

The *fibrous ring* from which the flaps take origin is involved in the inflammatory process. According to the measurements of Kirch,[23] the ring is dilated in mitral stenosis even though the orifice is extremely small; ring and orifice are connected by elongated flaps He considers this widening of the mitral ring as correlated with the dilatation of the left auricle In long-standing cases, there is often marked calcification of the ring.* While such calcification is much more common in the elderly, it is occasionally encountered in the young Rigid fibrosis and calcification probably interfere greatly with the systolic reduction in circumference and change in shape of the mitral orifice (page 398) and thus favor regurgitation Exceptionally, large calcareous masses in the mitral ring produce some stenosis.

Arteriosclerotic Mitral Lesions.—White and yellow patches of atheromatous and fibrous change on the ventricular side of the aortic flap of the mitral valve are present in almost all adults and many children, but do not impair the function of the valve The same is true of the more extensive atheromatous lesions of the mitral curtains found in many arteriosclerotic individuals. Extensive thickening and calcification, with or without atheromatosis, of the mitral ring and the base of the curtains, may also occur in individuals without other evidences of endocarditis In such cases, the lesion is to be regarded as "degenerative" in pathogenesis and allied to arteriosclerosis. That calcification of the mitral ring may also result from rheumatic infection was mentioned above. In many cases, even complete annular calcification of the mitral ring seems to do little harm to the function of the valve, and may be found at the necropsy of individuals who had no symptoms of heart disease The presumption that such annular sclerosis and calcification of the mitral ring may produce regurgitation through interference with the systolic diminution in size of the orifice has already been mentioned But it would appear that the purely arteriosclerotic lesions of the mitral valve, like those of the aortic, are rarely of clinical significance Injury to the bundle of His by extension of such a lesion has been reported by Moenckeberg [36]

The Chambers of the Heart in Mitral Disease.—The state of the left ventricle in mitral disease is largely dependent (apart from complication by aortic valvular or other lesions) on whether the patient passes through a long period of significant mitral regurgitation If such is the case, the left ventricle is hypertrophied and dilated, although rarely to so great an extent as in aortic disease

* Occasionally, calcification of the mitral ring (and of the aortic valve in calcific aortic stenosis) can be detected during life by careful fluoroscopic examination with a small diaphragm and rather hard rays (Marks[34])

On the other hand, the left ventricle is decreased in size in "pure" mitral stenosis, a fact which was long ago established quantitatively by Hirsch,[17] using the method of Mueller to weigh the individual parts of the heart, and more recently by the careful measurements of Kirch.[23] *Where tight mitral stenosis has existed from an early age,* the cavity of the left ventricle is very small and the walls thin, the apex of the heart may be formed by the enlarged right ventricle Kirch has shown that the atrophy of the left ventricle in mitral stenosis is confined to the inflow tract extending from the



Fig. 18 --Section through the enormously thickened endocardium of the left auricle in a patient with mitral stenosis, specific rheumatic inflammation with replacement by scar tissue

mitral valve to the apex, while the outflow tract from the apex to the aortic orifice is unaffected. The result of the elective atrophy with consequent shortening of the inflow tract is that the mitral valve assumes a *position much lower than normal* in relation to the aortic valve Kirch further found that as a result of the atrophy of the posterior wall of the left ventricle in mitral stenosis, the plane of the mitral ring becomes very oblique in relation to the long axis of the left ventricle, instead of almost perpendicular to it, as is normally the case.

The left auricle is enlarged in mitral disease. Both hypertrophy and dilatation are present in most cases. Not rarely, the left auricle is 5 mm. thick, and much greater hypertrophy has been observed In some cases, a most remarkable dilatation of the left auricle develops, as a result of which the chamber attains a capacity unparalleled, so far as I am aware, by any of the chambers of the heart under other circumstances, a volume of much over a liter has been observed repeatedly In such cases, the wall of the left auricle is very thin (apart from areas covered by clot), and the sections reveal that most of the wall is fibrous tissue containing only scattered muscle fibers The left auricle enlarges first posteriorly and then to the right, so that it forms, in the presence of great enlargements, at least part of the right border of the heart It is interesting that while great enlargement of the left auricle occurs predominantly in the presence of tight mitral stenosis, it is occasionally encountered where the stenosis is not extreme and regurgitation predominates The principal cause of the extraordinary dilatation of the left auricle in some cases of mitral stenosis is presumably the high pressure within the chamber. However, destruction of the muscle of the chamber by rheumatic inflammatory lesions and replacement by fibrous tissue is doubtless also important These rheumatic lesions of the wall of the left auricle were long ago observed by Huchard[20] and described in detail by MacCallum [30] They are present in a high proportion of cases of rheumatic mitral disease; in fact, by careful examination Gross[16] found left auricular lesions macroscopically in 87 per cent and microscopically in 100 per cent of rheumatic hearts The rheumatic left auricular lesions often exhibit a characteristic appearance. They generally appear first as a corrugated thickening of the posterior wall of the left auricle above the mitral valve and may extend to cover a large part of the chamber, even reaching the pulmonary veins. Histological examination (for details, see Gross) reveals the specific rheumatic nature of the lesion, which in the active state contains numerous Aschoff bodies, and heals in the form of a thick scar. The thrombi which are generally present in the left auricle in mitral disease are discussed later

Apart from unusual instances of death from independent causes or bacterial endocarditis in a perfectly compensated patient, the right ventricle and auricle are hypertrophied and dilated in mitral disease

MITRAL REGURGITATION

The Causes of Mitral Regurgitation.—Incompetence of the mitral valve may be merely one manifestation of dilatation of the left ventricle—functional mitral regurgitation—or a result of organic changes in the curtains, ring, chordæ tendinæ, or papillary muscles Functional mitral regurgitation is discussed in Chapter XXII and

in conjunction with the various conditions in which dilatation of the left ventricle occurs. Clinically significant mitral regurgitation is almost always due to rheumatic infection, and this section will be confined largely to lesions of this etiology. Scarlet fever is occasionally followed by mitral leaks; but the interrelationships of postscarlatinal and rheumatic valvular changes are close, and their identity not altogether excluded. Atherosclerosis is a common cause of mitral regurgitation; however, it would appear that although such a lesion is often documented by a loud murmur, the volume of regurgitation is so small as to be hardly significant in the pathogenesis of circulatory failure in arteriosclerotic and hypertensive heart disease. Much more important than the regurgitation due to atherosclerotic changes in the mitral valve is the functional regurgitation consequent on dilatation of the left ventricle when it fails as a result of hypertension and coronary artery disease. However, it is possible that calcification of the mitral ring may interfere with the systolic diminution in size of the mitral orifice (page 398) and thus favor regurgitation. The regurgitation that may result from the vegetations and valvular ulceration of bacterial endocarditis rarely contributes significantly to the clinical picture of the disease. Traumatic mitral regurgitation is a clinical curiosity.

Clinical Significance of Mitral Regurgitation.—In recent years, distinguished authorities, notably Lewis[27] and Cabot,[6] have minimized the significance of mitral regurgitation in the pathogenesis of cardiac failure in rheumatic heart disease. "Accurate diagnosis of disease of the mitral valve depends upon the recognition, not of mitral regurgitation but of mitral obstruction" (Lewis). The main grounds for this depreciation of the clinical importance of rheumatic mitral regurgitation are the following:

1. In former years, the diagnosis of mitral regurgitation was sometimes made solely on the basis of an apical systolic murmur. Individuals with such a murmur were rejected for military service despite the fact that they were not preternaturally breathless on exertion, the heart was not enlarged, and there was no history of rheumatic infection. Of course, such overemphasis of the apical systolic murmur is not to be defended; for many decades, every competent physician has recognized that such a murmur may be due to various causes other than mitral regurgitation, being often of cardiorespiratory origin and in no way portentous. But, on the other hand, the fact that many systolic murmurs are of little clinical significance does not mean that this is true of all. Actually, it is not rare to encounter individuals, especially children, in whom an apical systolic murmur is accompanied by so little supporting evidence of organic heart disease, that one is not justified at the time in maintaining such a diagnosis, and yet the subsequent course of events proves the latter to have been present.

2. Most patients with heart failure in whom examination reveals evidence of no lesion other than mitral regurgitation sooner or later develop the signs generally taken to indicate mitral stenosis (page 514). And in the large majority of *adults* with rheumatic disease of the mitral valve who succumb to heart failure, stenosis is found at necropsy in addition to incompetence. But neither of these facts negates the frequent significance of regurgitation in the production of heart failure. They do not indicate that at an earlier stage of the disease, when stenosis was absent or insignificant, the regurgitation did not throw a great burden on the heart. That the latter is actually the case is indicated especially by necropsy observations on children succumbing to heart failure of rheumatic causation, in whom one often finds severe incompetence of the mitral valve in the absence of stenosis and accompanied by great hypertrophy and dilatation of the left ventricle and auricle Recent observations have shown that the opinion formerly held that rheumatic mitral regurgitation without stenosis is a great rarity at necropsy is erroneous. Thus, in 100 postmortem examinations on individuals who succumbed to rheumatic heart disease before the age of twenty-one years, Bland, White and Jones[3] observed 25 in which the mitral valve was deformed but there was no anatomical stenosis. Dana and Reidy[10] found that one-half of all cases of rheumatic endocarditis of the mitral valve (ages not given) show no stenosis at necropsy, even in cases known to have been of many years' duration. While in my experience the large majority of adults with dynamically significant rheumatic mitral disease have revealed both incompetence and stenosis at necropsy, I have seen several instances of practically pure mitral regurgitation.

To the writer, as to Sprague and White,[44] it seems that the pendulum has swung too far against the diagnosis of rheumatic mitral regurgitation, and the rôle of mitral leaks in the production of heart failure has been excessively depreciated. To a certain extent this is doubtless a justifiable reaction against the facile diagnosis of organic heart disease on the basis of merely a systolic murmur. In the pathogenesis of the failure of the rheumatic heart, various factors are summated—myocardial implication, the mechanical effects of valvular defects, and often pericardial disease. Among these, the mechanical consequences of mitral incompetence are often significant, in ways that will be discussed in the next section. There are many cases in which judicious evaluation of the history, the physical findings, and especially the roentgen examination of the size of the individual chambers enables one to state with fair assurance that mitral regurgitation is present, and that at the time mitral stenosis is either minimal or not functionally significant According to the postmortem observations of Bland, White and Jones, mitral stenosis rarely develops before the third year after

the onset of rheumatic infection. It should always be borne in mind that rheumatic heart disease generally progresses through multiple individual exacerbations, and that at one stage mitral regurgitation may be significant and accompanied by hardly any stenosis, subsequently, the latter develops and, while diminishing the regurgitation, itself throws a new and perhaps more severe handicap on the heart.

Pathological Physiology.—It is not feasible to measure the volume of regurgitation in mitral leaks. The postmortem appearance of the valve would indicate that the leak may vary from a minute defect which can be of little functional significance to one in which the mitral curtains are so retracted and immobile that regurgitation must be almost as free as if the flaps were absent. However, postmortem observations do not take into account the rôle of the muscle in regulating the form and circumference of the mitral orifice (page 398), so that the curtains can effect faultless closure In many instances of rheumatic heart disease, mitral regurgitation may well be due not only to changes in the valve but also to dilatation of the muscle In experimental mitral leaks, Straub[46] found that the regurgitation may amount to 52 per cent of the systolic discharge.

Light has been thrown on the phases of the cardiac cycle in which regurgitation occurs by the animal experiments of Wiggers and Feil.[49] They found that there is very little regurgitation during the period of isometric contraction of the ventricles prior to the opening of the sigmoid valves. This they attribute to the shortness of the isometric phase (0.05 second) and the relatively low intraventricular pressure during this early phase of systole, as a result of which the inertia of the blood within the ventricle is hardly overcome Wiggers and Feil found that regurgitation does not begin to be significant until the period of ejection, and that it lasts not only through this period but also 0 08 to 0 09 second into diastole, when the auriculo-ventricular valves open. They further showed that, contrary to what had previously been assumed, the duration of neither the isometric contraction nor the ejection phase of ventricular systole is altered in mitral insufficiency.

On the basis of the experimental findings of Wiggers and Feil, Straub, and others, the process of circulatory adjustment in mitral regurgitation would seem to be about as follows: When the regurgitation first develops, the systolic discharge into the aorta decreases by the volume of the regurgitated blood. This volume is added to the blood that enters the left auricle from the pulmonary veins The left auricle and large pulmonary veins are thus distended and the pressure within them elevated. The result is that when the mitral valve opens, diastolic filling of the left ventricle takes place under greater pressure and the diastolic volume of the chamber is

increased. In accord with Starling's law of the heart, the succeeding systole is more powerful and the systolic discharge is augmented. While part of this regurgitates into the left auricle, the volume that is ejected into the aorta is also increased. By this mechanism, circulatory compensation is attained in the sense that the systolic discharge into the aorta returns to normal. But the compensation involves increased work for both the left ventricle and the left auricle. For the left ventricle must eject not only its usual stroke volume into the aorta but also the regurgitant stream into the left auricle. And the left auricle must eject, in addition to its normal stroke volume, that portion of the regurgitated blood which does not re-enter the left ventricle prior to auricular systole purely as a result of the higher pressure within the left auricle and pulmonary veins Moreover, there is good reason to believe that the intraventricular tension against which the auricle must empty is abnormally high The result is that in mitral regurgitation there is initial dilatation of both the left ventricle and the left auricle, and that hypertrophy of both these chambers gradually develops.

The effect of mitral regurgitation on the pulmonary circuit and the right ventricle has been investigated on a number of occasions Straub found that the volume of blood in the lesser circulation increases following the production of mitral regurgitation; in his acute experiments, this pulmonary engorgement was at the expense of a decrease in the volume of blood in the systemic circulation. It would appear that as long as the mitral regurgitation is completely compensated by the mechanism described in the preceding paragraph, the engorgement affects only the *venous* half of the pulmonary circuit, the regurgitated blood being accommodated by dilatation of the left auricle and pulmonary veins This conception is supported by the finding of MacCallum and McClure,[11] Straub, and Wiggers and Feil that in well-compensated mitral regurgitation the pressures in the pulmonary artery and the right ventricle do not rise above those present prior to the induction of the valvular defect Evidently, as long as mitral regurgitation is compensated, the pressure in the left auricle and pulmonary veins is elevated during too short a fraction of the cardiac cycle to influence appreciably the tension in the pulmonary artery. But this state of affairs obtains only as long as the functional capacity of the left side of the heart is sufficient to compensate for the regurgitation by the mechanism described above. As soon as the left side of the heart fails, the pressure in the right ventricle rises (Wiggers and Feil), indicating that the engorgement has extended upstream to the pulmonary artery with consequent rise of pressure within that vessel. In other words, the experimental findings indicate that mitral regurgitation *per se* produces engorgement of only the venous portion of the pulmonary circuit; only when the left

side of the heart weakens does the arterial portion of the pulmonary circuit become engorged with consequent hypertension in the pulmonary artery and increase in the work of the right ventricle. In the following section, it will be seen that the same is apparently true of clinical mitral regurgitation.

The Compensated Stage of Mitral Regurgitation.—Rheumatic mitral regurgitation may be so well compensated that the bearer is capable of hard work for many years, and may never develop heart failure. Unequivocal examples of such a state of affairs, like the following, are not uncommon: The patient is observed early in a bout of rheumatic fever, and careful auscultation reveals no murmurs. An apical systolic murmur appears, becomes louder, and persists after defervescence. Nevertheless, the individual feels entirely well, cyanosis is absent, and dyspnea is not more than usual after even vigorous exercise. In such cases, even careful roentgenological study of the heart may reveal no definite enlargement of any of the chambers or change in the amplitude of their pulsation. The heart rate is normal, the pulmonic second sound is not accentuated, the lung fields are not engorged, the pulmonary circulation time is normal, and the electrocardiogram is not unusual. The only evidence of mitral regurgitation is the murmur, the organic nature of which would be uncertain had its evolution not been observed. In these cases, it is to be presumed, the volume of regurgitation is small. Such lesions are observed at necropsy only accidentally, when the individual succumbs to some independent cause, and the slight or moderate retraction and thickening of the mitral curtains or shortening and fusion of the finer chordæ tendinæ are found. The clinical significance of such perfectly compensated mitral regurgitation is little more than that it indicates the bearer is predisposed to further attacks of rheumatic fever or subacute bacterial endocarditis, and that the heart deserves more than the usual attention under strains like pregnancy, surgical operations or acute infections.

In other cases of well-compensated mitral regurgitation, there is definite enlargement of the left auricle and ventricle. (See next section.) Exertional dyspnea, cyanosis, tachycardia, and objective evidence of pulmonary engorgement may be absent even though the apex beat is well outside the mid-clavicular line and in the sixth interspace. Despite such enlargement, compensation may continue to be excellent for years. However, enlargement sufficient to be demonstrable by palpation and percussion is to be regarded as evidence that the compensatory mechanisms are being strained, and heart failure is an ever-present danger.

Heart Failure in Mitral Regurgitation.—This valvular defect increases the work of the left auricle and left ventricle. The increment in work is performed through the intermediary of compensa-

tory dilatation and hypertrophy of both chambers Sooner or later, these compensatory mechanisms fail, the left side of the heart becomes insufficient, and engorgement of the pulmonary circuit results. However, the situation is complicated by the fact that in the large majority of rheumatic lesions of the mitral valve in adults, more or less stenosis develops before heart failure appears. Both the regurgitation and the stenosis then play their respective parts in the pathogenesis of the heart failure, and their relative significance varies in different instances. Sometimes, mitral stenosis develops early and the orifice is so constricted as to preclude significant regurgitation, the so-called pure mitral stenosis (page 492). In other patients, there is a long period of mitral regurgitation, and only after years of repeated attacks of rheumatic fever do evidences of stenosis appear; even at necropsy, regurgitation may still be the predominant or even, especially in children, the sole, lesion. But whether regurgitation or stenosis is the more significant, the general pattern of the circulatory failure is the same; namely, an initial stage of insufficiency of the left side of the heart with symptoms of pulmonary engorgement, followed, if the patient does not succumb during this period, by failure of the right heart with systemic venous engorgement. In order to avoid repetition, this clinical picture of the circulatory failure of "mitral disease" will be described in the section on Mitral Stenosis (page 503).

Here it may be pointed out, as already emphasized by Sprague and White, that in a patient with auscultatory signs of both mitral insufficiency and stenosis, the size of the left ventricle often affords an excellent criterion of which lesion is predominant in a functional sense. When mitral stenosis develops early in rheumatic heart disease and there is little opportunity for significant regurgitation, the left ventricle is not enlarged and may even be atrophied (page 492). The normal or small size of the left ventricle in these cases of "pure" mitral stenosis contrasts sharply with the usually huge left auricle. On the other hand, if the patient has gone through a long period of significant mitral regurgitation, the left ventricle is enlarged, often greatly so. And even the subsequent development of a tight mitral stenosis, which must reduce the volume of regurgitation greatly, does not result in the disappearance of the enlargement of the left ventricle due to the antecedent period of regurgitation—a fact which I have several times verified at necropsy.

The enlargement of the left ventricle due to mitral regurgitation differs from that in hypertension and aortic valvular disease in that it is not initiated selectively in the outflow tract (page 298), but apparently starts subjacent to the mitral valve and involves the entire left ventricle from an early period. The result is that both the transverse and longitudinal diameters of the chamber are

increased, the apex being displaced outward and downward. In many cases of mitral regurgitation, the roentgen-ray picture shows a well-marked, shoulder-like prominence of the upper portion of the left border of the left ventricle, so that the chamber appears to be enlarged upward and to the left. This shadow often merges above with the shadow of the enlarged left auricular appendage and sometimes, also, when the left side of the heart has failed, with the shadows of the enlarged conus of the right ventricle and, more cephalad, the dilated pulmonary artery. The bulging of the upper portion of the left ventricular shadow in the roentgen-ray corresponds to dilatation of the portion of the left ventricle adjacent to the mitral valve, which may be quite prominent at the necropsy of an individual with free mitral regurgitation. Examination of the retrocardiac space may reveal a bulging of the left auricle in patients with predominant mitral regurgitation, but this is not so marked as in most cases in which stenosis is the dominant lesion If the left side of the heart has failed with resultant pulmonary engorgement, enlargement of the right ventricle and perhaps the right auricle occur whether stenosis or regurgitation is the predominant lesion of the mitral valve

MITRAL STENOSIS

In the preceding sections, we have seen that in the large majority of instances of rheumatic disease of the mitral valve in adults, stenosis sooner or later becomes the preponderant defect. However, it was also pointed out that for a long period before the constriction attains significance, regurgitation may have been consequential as documented by great enlargement of the left ventricle. Apart from the exceptional cases in which stenosis evolves with little regurgitation—the cases of "pure" mitral stenosis with a small left ventricle—regurgitation and stenosis participate hand in hand in the pathogenesis of the ultimate circulatory failure, and it is really the clinical picture of the combined lesion that will be described in this section.

The pathological anatomy of mitral stenosis has already been discussed.

Pathological Physiology of Mitral Stenosis.—Narrowing of the mitral orifice must be very pronounced before it produces a significant mechanical obstacle to the circulation. Thus, in experiments with a mechanical circulation model, Allan[1] found that "Narrowing of the mitral orifice to one-quarter of its size reduces the inflow to the ventricle a little, and this reduction is easily overcome by a small rise in the head of pressure." Not rarely, one finds well-marked mitral stenosis at the necropsy of an individual who had no symptoms of circulatory failure. The mechanisms

which tend to overcome mitral obstruction will be considered in the following:

The filling of the left ventricle does not proceed with equal speed throughout its diastole There is first a phase of rapid filling early in diastole, then the period of diastasis in which little blood passes from the auricle to the ventricle, and finally another period of more copious filling of the ventricle due to the systole of the auricle. *A priori*, therefore, although this conception is not yet established experimentally, it would seem that the first effect of progressive constriction of the mitral orifice would be merely a *prolongation of the initial period of ventricular filling at the expense* of diastasis. The velocity of ventricular filling would thus be less, but would be atoned for by prolongation of the initial period of ventricular filling into diastasis Moreover, Katz and Siegel[21] have found that the duration of ventricular systole is decreased in experimental mitral stenosis, which also tends to prolong the time available for diastolic filling of the ventricle With still greater constriction of the mitral orifice, this mechanism of prolongation of early diastolic filling into diastasis would no longer suffice and the left auricle would be preternaturally distended at the onset of auricular systole According to Starling's law of the heart, this distention of the auricle evokes a more powerful systole of the chamber, with the result that the larger volume of blood is ejected into the ventricle despite the greater resistance due to the mitral obstruction. In brief, it would appear that the initial mechanisms tending to overcome constriction of the mitral orifice are: (1) Prolongation of the initial period of ventricular filling into diastasis, and (2) more powerful contraction of the left auricle through the intermediacy of dilatation and ultimately hypertrophy of the chamber.

As long as these mechanisms *per se* suffice to maintain the volume of ventricular filling, the effects of the mitral obstruction on the pulmonary circuit are not great. Straub[46] has found that under such conditions, the pressures in the pulmonary artery and right ventricle are not elevated despite an increase in the total volume of blood within the pulmonary circuit; evidently, the increment in the blood content of the pulmonary vessels is accommodated in the venous half (page 210). But the experiments of Gerhardt[14] show that if the stenosis is of sufficiently high degree, or the total blood volume is elevated by means of an intravenous infusion, the engorgement of the pulmonary circuit becomes so marked that it is no longer confined to the venous half and the pressure in the pulmonary artery rises, with resultant increase in the work of the right ventricle In Gerhardt's experiments, when the pressure in the left auricle exceeded about 7 cm of water, the tension in the pulmonary artery rose. A rise in the pressure in the left auricle

of some such order doubtless occurs in human mitral stenosis when the compensatory mechanisms described in the preceding paragraph fail. Then the engorgement of the pulmonary circuit extends to the pulmonary artery with resultant increase in the work of the right ventricle, which is performed by means of dilatation and hypertrophy of this chamber.

From the point of view of circulatory dynamics, then, one might anticipate three stages of mitral stenosis:

1. An initial stage of faultless compensation, in which prolongation of ventricular filling into diastasis and increased work of the left auricle maintain the rate of filling of the left ventricle. There is no engorgement of the arterial side of the pulmonary circulation and consequently no hypertrophy of the right side of the heart.
2. A stage of failure of the left side of the heart with pulmonary engorgement, hypertension in the pulmonary artery, and resultant hypertrophy of the right ventricle.
3. A terminal stage of failure of the right side of the heart in which systemic venous engorgement is superadded to the antecedent congestion of the lesser circulation.

In the majority of cases of mitral stenosis, the succession of these three stages can be traced That this usual "natural history" of mitral stenosis may be interrupted at any stage by embolism or other complication goes without saying. Further, there are also many patients in whom decompensation is initiated by the manifestations of the third stage, without a clinically discernible intermediate phase of isolated insufficiency of the left side of the heart; as will be pointed out below (page 504), this is usually due to the precipitation of heart failure by the development of auricular fibrillation in a previously well-compensated patient.

The Compensated Stage of Mitral Stenosis.—Occasionally, auscultation yields unequivocal evidence of mitral stenosis in an individual who is not short of breath or cyanotic, and may not even be aware that he has a cardiac lesion. Such excellent compensation for mitral obstruction may last for a long time. Thus, I had under my care for more than eight years a man, aged sixty years, with a rumbling apical murmur lasting throughout diastole and terminating in seemingly crescendo fashion in a snappy first sound; this murmur was detected forty years before, and yet the man had never had any cardiac symptoms. Notwithstanding such cases, protracted faultless compensation is not nearly as common in mitral stenosis as the same state of affairs in aortic valvular lesions of mitral regurgitation. This has been attributed to the fact that the compensation of mitral stenosis is not carried out by the powerful left ventricle, as in the case of the other lesions.

In most of the totally asymptomatic cases of mitral stenosis that I have seen, the pulmonic second sound has not been accentuated,

and fluoroscopic examination revealed little, if any, enlargement of the left auricle or right ventricle, and no evidence of pulmonary engorgement. Presumably, such findings most often indicate that the stenosis is not marked. However, it is not very rare to be surprised at necropsy by tight mitral stenosis which apparently had given no symptoms during life. Perhaps in such cases the stenosis evolves so slowly after a single attack of rheumatic fever that opportunity is afforded for hypertrophy to substitute for dilatation of the left auricle when the latter is of relatively slight degree, and the hypertrophy compensates for the stenosis so effectively that pulmonary engorgement is averted.

Even though the patient with mitral stenosis is so well compensated, nevertheless he, or more often she, is threatened by various dangers. Among these is the development of subacute bacterial endocarditis—a complication that, for reasons which have not been elucidated, threatens mostly individuals without heart failure (Libman[29]). Also, although this is rare in well-compensated cases with regular rhythm, thrombi from the left auricle may embolize with resultant hemiplegia or other manifestation. Paroxysmal or permanent auricular fibrillation or flutter may develop without impairing the state of compensation; the change in rhythm may be apparent only to the physician, or the rapid or irregular heart action may be evident to the patient. Respiratory infections are more apt to be followed by bronchopneumonia or bronchitis in individuals with even well-compensated mitral stenosis than in those without a cardiac lesion.

Much more common in mitral stenosis is a state of tolerable, though not faultless, compensation. While the capacity for exercise is definitely diminished, it is nevertheless sufficient to permit an occupation which is not arduous, the performance of housework, or passing through pregnancies. Usually, slight cyanosis is present and produces the "mitral flush" on the malar eminences which may reveal the condition at a glance. The pulmonic second sound is accentuated; enlargement of the left auricle and right ventricle may be demonstrable; and the pulse is often small. It is evident in such cases that the pulmonary circuit is engorged, with rise in pressure in the pulmonary artery, and the second line of defense in the form of dilatation and hypertrophy of the right ventricle has been called into action While this state of affairs may continue for a number of years, nevertheless it constitutes the transition to decompensation, and the patient is always in danger.

The General Course of Heart Failure in Mitral Stenosis.—As might be anticipated, circulatory failure in mitral stenosis is generally initiated as isolated insufficiency of the left side of the heart Dyspnea, less often cough or hemoptysis, ushers in the heart failure, and the objective findings are confined to cyanosis and other conse-

quences of pulmonary engorgement. In contrast, the systemic veins are not engorged, the liver is not swollen and there is no edema. This stage of isolated left heart failure may last from a short time to many years, with or without exacerbations and remissions. Exceptionally, death occurs during this phase of left-sided failure from bronchopneumonia or other complications of pulmonary engorgement, as a result of embolization of thrombi from the left auricle, from subacute bacterial endocarditis, or from intercurrent ailments

Much more often, however, the patient reaches a second stage of heart failure marked by the superimposition of insufficiency of the right ventricle on the pre-existent left-sided failure. Clinically, this is documented by engorgement of the systemic veins, drawing in its wake swelling of the liver, edema and serous effusions. That most patients with mitral stenosis ultimately develop insufficiency of the right ventricle is not surprising, for this valvular lesion is the cause *par excellence* of marked and protracted hypertension of the lesser circulation. In no other condition does one encounter such loud accentuation of the pulmonic second sound, testifying to the high tension in the pulmonary artery against which the right ventricle must empty. And at the necropsy of one who has long suffered from mitral stenosis, the atheromatous and sclerotic changes in the pulmonary arteries and veins and the hyalinization of the pulmonary arterioles—in sharp contrast to the absence of these lesions in the aorta and its tributaries—bear witness to the long-standing hypertension of the lesser circulation. In mitral stenosis, the right ventricle is confronted by much the same task as the left ventricle in systemic hypertension, and sooner or later gives way.

The large majority of patients with mitral stenosis run the course just described, namely, initiation of cardiac failure as isolated insufficiency of the left side of the heart with subsequent development of right ventricular failure. Even when the patient first presents herself because of swelling of the feet or another symptom of right-sided failure, careful interrogation almost always elicits previous dyspnea on exertion. Exceptionally, however, the circulatory failure of mitral stenosis is ushered in abruptly with a symptomatology including such characteristic manifestations of right ventricular insufficiency as swelling of the systemic veins, rapid enlargement of the liver, and dependent edema. In such cases, the heart failure is generally precipitated by the onset of auricular fibrillation. This arrhythmia may diminish the output of the right ventricle so greatly that, despite the equal impairment of the left ventricle and the presence of the mitral obstruction, so little blood is pumped per minute from the venæ cavæ to the pulmonary circuit that the manifestations of pulmonary engorgement are relatively slight in comparison to those of systemic venous engorgement.

The Individual Symptoms of Heart Failure in Mitral Stenosis.—*Dyspnea.*—Almost every patient with mitral stenosis suffers from dyspnea at one period or another of the disease. The dyspnea is nearly always exertional. While the shortness of breath on exercise may be accompanied by nocturnal paroxysms of cardiac asthma, it is rare in mitral stenosis, contrary to arteriosclerotic or hypertensive heart disease, for paroxysmal dyspnea to occur when exertional dyspnea is slight.

Shortness of breath on exertion is the most common initial symptom of mitral stenosis, and generally the one which brings the patient to the physician. Further, as already mentioned, when swelling of the feet or some other symptom is the principal complaint, questioning usually reveals that the capacity for exercise had previously been restricted by dyspnea. Most often, the dyspnea is insidious in onset, and at first noticed only on climbing stairs or some unwonted exertion. Such slight dyspnea on exertion may be the only complaint for years, even decades. When mitral stenosis dates back to youth, the patient may state that she has "always" been short of breath, and usually has unconsciously adjusted her way of life to what she considered merely one aspect of the general weakness and retardation of development from which these patients suffer. On the other hand, the dyspnea may set in acutely and violently, this is especially apt to be the case when heart failure is precipitated by auricular fibrillation, during pregnancy, or by overexertion Rapid aggravation of dyspnea in mitral stenosis may be due to various causes, notably change in rhythm, hydrothorax, such pulmonary complications as bronchopneumonia, infarction, or edema, exacerbation of rheumatic fever, development of pericarditis, or massive thrombosis in the left auricle Sudden swelling of the liver may render breathing very painful and thus augment dyspnea

In a general way, the dyspnea of mitral stenosis parallels the severity of the pulmonary engorgement. Very intense dyspnea is often encountered in patients with isolated failure of the left side of the heart and no systemic venous engorgement In such patients, the dyspnea may become much less agonizing when the right ventricle gives way with engorgement of the venæ cavæ and their tributaries, objectively, they are worse, but subjectively they feel better for the time being

Orthopnea almost always accompanies dyspnea of any considerable severity in mitral stenosis Indeed, patients with relatively slight dyspnea on exertion and able to attend to business may need several pillows at night; this state of affairs may continue for years.

Cough is a common complaint in mitral stenosis and may be very severe. Most characteristic is a cough which is brought on by exertion. But very often the cough occurs in paroxysms with no

obvious relation to exercise, and it may be worse at night. The cough is most often a manifestation of insufficiency of the left side of the heart and results from bronchial and pulmonary engorgement (page 213). However, in some cases the cough is probably due to pressure on the main bronchi by the dilated left auricle, which is often evident in the roentgenogram. The cough may be dry or productive, the characteristics of the expectoration, which may be bloody, have already (page 214) been described. The cough is often worse in winter and alleviated by a warm climate; presumably, secondary bronchial infection readily develops on the basis of the engorgement. Rarely, cough indicates the onset of a paroxysm of pulmonary edema. The cough, expectoration, and hemoptysis lead not infrequently to a mistaken diagnosis of tuberculosis or "bronchitis" in cases of mitral stenosis. In such instances the shadows in the roentgen-ray picture due to pulmonary engorgement have been mistaken for tubercles, an error which should hardly occur.

Hemoptysis is a common manifestation of pulmonary engorgement in mitral stenosis and may be the initial symptom of the disease. The blood spitting ranges from merely streaky sputum to massive hemorrhages, which may even be fatal (page 215). A patient who has once had hemoptysis in mitral stenosis tends to have it repeatedly, while other individuals never expectorate blood despite intense pulmonary engorgement. Hemoptysis other than that due to gross infarction is even more common during the stage of isolated or preponderant insufficiency of the left side of the heart than after the right ventricle has given way with resultant systemic venous stasis. I have twice seen hemoptysis first appear after successful digitalization in patients with mitral stenosis and auricular fibrillation had cleared up systemic venous stasis. These phenomena are presumably correlated with the rôle of hypertension of the lesser circulation in producing the hemoptysis of mitral stenosis. Some patients have several massive hemoptyses at considerable intervals, while between the hemorrhages they are able to be up and about with no other complaint than that of dyspnea on exertion. The pathogenesis of hemoptysis in pulmonary engorgement has already been discussed (page 216).

Palpitation probably ranks next to dyspnea in frequency among the symptoms of mitral stenosis. It may occur with either regular or irregular rhythm. The consciousness of the heart's action generally first appears after exertion or excitement, but may occur at rest; some patients are disturbed by it only when in bed at night. Palpitation may be especially annoying at the onset of auricular fibrillation, before the patient has become accustomed to the new rhythm. On the other hand, there are many individuals with

auricular fibrillation, even with a rapid rate, who are not aware of the irregularity of the heart's action.

Precordial pain is rarely a prominent constituent of the clinical picture of mitral stenosis However, some of the patients complain of pain, usually described as an ache, after exercise. Sometimes, there is a continuous ache. Severe anginal attacks are extremely rare, and generally indicate complication with coronary arteriosclerosis or aortic valvular disease. The rarity of anginal pain in relatively pure mitral stenosis, despite the frequently small cardiac output is perhaps accounted for by the small size of the left ventricle, as a result of which myocardial ischemia does not readily occur. Sternberg[45] has described a case of mitral stenosis with angina pectoris, in which he attributed the pain to compression of the left coronary artery by the dilated left auricle, the explanation seems scarcely convincing. Another ingenious, but unsupported, hypothesis is that of Hochrein and Eckardt,[18] who suggest that anginal attacks in mitral stenosis may be due to shortening of the chordæ tendinæ, which results in traction on the aortic flap of the mitral valve and through it on the left sinus of Valsalva, thereby narrowing the mouth of the left coronary artery. On extremely rare occasions, the onset of auricular fibrillation or paroxysmal tachycardia is accompanied by violent cardiac pain. I saw a man in his thirties with a history of long-standing but well-compensated valvular disease, who was admitted to the hospital with agonizing precordial pain and symptoms of shock, in consequence of which a diagnosis of coronary thrombosis had been made. He had auricular fibrillation with an extremely rapid ventricular rate. Digitalization quickly slowed the heart with complete disappearance of the anginal pain within twenty-four hours. Then it was found that he had mitral stenosis, but there was also a second diastolic murmur of aortic regurgitation.

Occasionally, patients with mitral stenosis complain of an ache between the left scapula and the spine; there may be tenderness in this area. Vaquez[47] attributes these phenomena to pressure by a dilated left auricle.

When the right ventricle fails, swelling of the liver may give rise to pain, tenderness and rigidity in the right upper quadrant and epigastrium. If the distention is rapid and marked, as at the onset of auricular fibrillation, the pain may be very severe and accompanied by vomiting; such cases have been confused with gall-stone colic. The pain of a distended liver may radiate to the right scapula and shoulder.

Hoarseness due to paralysis of the left recurrent laryngeal nerve is a rare symptom of mitral stenosis. Ortner,[37] who originally described the phenomenon, attributed it to compression of the nerve by the dilated left auricle. This explanation was disproved

by the careful anatomical studies of Fetterolf and Norris,[13] who showed that the nerve is compressed by the left pulmonary artery. On the basis of observations on 3 cases of left recurrent laryngeal palsy in the left ventricular failure of arteriosclerotic heart disease, King, Hitzig and the writer[22] believe that this palsy in mitral stenosis also is a symptom of high tension in the pulmonary artery due to insufficiency of the left side of the heart. The high pressure in the left pulmonary artery produces a dynamic dilatation of the vessel, as a result of which the left recurrent laryngeal nerve is compressed as it passes through the triangle bounded by the left pulmonary artery, the arch of the aorta, and the ductus arteriosus.

On very rare occasions, *dysphagia* of slight degree results from compression of the esophagus by the dilated left auricle. However, in the vast majority of instances in which compression of the esophagus by the left auricle is demonstrable fluoroscopically after the administration of barium, subjective disturbances of deglutition are not present.

Weakness is a common symptom, even when the mitral obstruction is sufficiently well compensated to enable the patient to be up and about. Not rarely, a girl or young woman complains of weakness, and unsuspected mitral stenosis is found. In these patients, if the mitral stenosis has been present since early life, there are often evidences of "cardiac infantilism" in the form of retardation of the development of the secondary sexual characteristics and skeleton

Menstrual disturbances are very common in women with mitral stenosis.

Cyanosis is very frequent in mitral obstruction. Even when able to be up and about, many of the patients exhibit a bluish-red tinge of the malar eminences and cyanotic lips—the mitral facies. Slight or moderate cyanosis may persist for years. The cyanosis may be combined with slight jaundice—cyanotic icterus. Chronic cyanosis in patients whose dyspnea is not severe enough to keep them in bed is probably due to interference with gas exchange by alterations in the pulmonary capillaries and alveolar walls resulting from long-standing engorgement of the lungs, and which appear at the necropsy table in the form of brown induration (page 210). The preponderantly pulmonary origin of the cyanosis in many of these cases is indicated by the decreased oxygen saturation of the arterial blood and by the alleviation of the cyanosis in the oxygen tent. However, in an investigation of 20 cyanotic patients with mitral stenosis, Cossio and Berconsky[9] found that augmented delivery of oxygen in the capillaries was always associated with the pulmonary factor in the production of the cyanosis and that in some of the cases the peripheral mechanism was alone responsible for the discoloration. Predominance of cyanosis over dyspnea presumably indicates that at

the time interference with the aeration of the blood is relatively more significant than is elevation of pressure in the pulmonary circuit With severe heart failure, the cyanosis may become very intense Infarction, bronchopneumonia, and pulmonary edema are common causes of rapid aggravation of cyanosis in mitral stenosis. The remarkable cyanosis that results from occluding thrombi in the left auricle will be discussed below



Fig 19 —Pulmonary engorgement in a patient with mitral stenosis, auricular fibrillation and hemoptysis The area of increased density under the right clavicle simulating a tuberculous infraclavicular lesion cleared up after three days of bed rest and digitalization

Pulmonary engorgement is an immediate and constant consequence of heart failure in mitral stenosis The manifestations of pulmonary engorgement dominate the clinical picture throughout the course of almost every case of mitral stenosis, and most of the patients ultimately succumb to one of the complications of pulmonary engorge-

ment—bronchopneumonia, pulmonary edema, or infarction. The clinical picture of pulmonary engorgement and of these complications has already been described (Chapters XIII and XIV). It should always be borne in mind in evaluating the status of a patient with mitral stenosis that there may be intense pulmonary engorgement with few physical signs Especially worthy of emphasis is that râles at the bases are not always present in even severe passive congestion of the lungs. Accentuation of the pulmonic second sound in mitral stenosis indicates a considerable degree of pulmonary engorgement, for it shows that the tension in the pulmonary artery has risen, and we have seen (page 501) that rise of pressure in the pulmonary artery does not result from mitral obstruction *per se*, but indicates insufficiency of the left side of the heart Fluoroscopic and roentgenographic examination of the hilus shadows and lung fields often reveals severe pulmonary engorgement when it is not evident from the physical examination Measurement of the pulmonary circulation time (page 55) and the vital capacity often affords valuable information regarding the severity of pulmonary engorgement in mitral stenosis. We have repeatedly alluded to the striking fact that the clinical manifestations of pulmonary engorgement—dyspnea, orthopnea, and hemoptysis—may be most severe during the stage of isolated insufficiency of the left side of the heart, and become much less severe when the right ventricle fails with resultant engorgement of the systemic veins and liver.

Pulmonary edema and cardiac asthma in mitral stenosis have been discussed in Chapters VIII and XIV. Here it may be repeated that the chief danger of acute and massive pulmonary edema in mitral stenosis—which is rare—is during pregnancy or following an unusual exertion

The Heart.—The changes in the morphology of the heart produced by mitral stenosis are generally characteristic. However, they are most often not demonstrable by percussion, and are then first revealed by fluoroscopic examination.

In most well-compensated cases of mitral stenosis, as well as many of those with severe heart failure, even skilful *percussion* reveals no definite abnormality in the cardiac borders The reason for this relative importance of percussion in mitral stenosis is that *the first effect of mitral obstruction on the heart is dilatation* and hypertrophy of the left auricle Since enlargement of this chamber occurs almost entirely deep in the thorax posterior to the rest of the heart (page 371), it cannot be demonstrated by percussion of the anterior surface of the chest While the tip of the dilated left auricular appendage may approach the anterior chest wall, this is hardly demonstrable by percussion On extremely rare occasions, great dilatation of the left auricle produces an area of dulness poste-

riorly between the spine and the scapula. When the anterior percussion outline of the heart is altered in mitral stenosis, it indicates, apart from complication by aortic valvular or other disease, one or more often both of two things:

1. That the left ventricle is enlarged as a result of a long period of dynamically significant mitral regurgitation prior to or *pari passu* with the evolution of the stenosis. Then the heart is enlarged downward and to the left It is to be borne in mind that when stenosis has been the preponderant lesion of the mitral valve almost from the start, the left ventricle is not enlarged and may be atrophied

2. That the right ventricle and perhaps also the right auricle is enlarged. Enlargement of the right ventricle begins in the region of the pulmonary conus and this result in outward extension of the cardiac dulness in the third left interspace—but such demonstration of "mitralization" by percussion has seemed to me rarely, if ever, unequivocal. When sufficiently marked, enlargement of the right ventricle results in increase in the right and left maximum transverse diameters of the heart. The dilatation of the right auricle which follows dilatation of the right ventricle further displaces the right border to the right. With pronounced hypertrophy of the right ventricle, there may be a powerful precordial heave over the chamber and epigastric pulsation.

Roentgenological examination is usually very informative and occasionally establishes the diagnosis of mitral stenosis when this is not otherwise feasible. The roentgen picture of the heart varies with the progress of the cardiac failure. In a broad way, three "roentgen stages" of mitral stenosis may be differentiated

1. There are exceptional instances of mitral stenosis, definitely proved by auscultation, in which careful roentgenological examination reveals no abnormality of the cardiac contours. These patients are almost always well compensated, evidently this is accomplished by hypertrophy with so little dilatation of the left auricle that enlargement of this chamber cannot be demonstrated *in vivo,* although practically always found at postmortem

2. Much more often, roentgenological examination reveals the changes in the cardiac contour resulting from enlargement of the left auricle. The patients in whom dilatation of the left auricle but not enlargement of the right ventricle can be shown by roentgen-ray examination may be quite well compensated, or they may suffer from dyspnea and other consequences of failure of the left side of the heart The enlargement of the left auricle may be revealed on dorso-ventral illumination by straightening or even bulging of the recess on the left border of the cardiac shadow above the left ventricle; this is due to enlargement of the left auricular appendage, the density of which may be enhanced by organized thrombi. In other cases, dorso-ventral illumination reveals no definite abnor-

mality despite considerable enlargement of the left auricle. The dilatation of this chamber is demonstrated by examination of the retrocardiac space with the patient's right shoulder to the screen; the dilated left auricle then bulges into the clear retrocardiac space. For details of the findings, the reader is referred to page 371. If the left ventricle is enlarged, this indicates a considerable preceding stage of significant mitral regurgitation or some other complication In the cases of relatively "pure" mitral stenosis seen mostly in young girls, the left ventricle is not enlarged; indeed, atrophy of the chamber may be evident from the roentgen findings.

3. In the third group of cases, enlargement of the right ventricle and perhaps also of the right auricle is added to the enlargement of the left auricle. Symptoms of heart failure are present, although they may consist only in dyspnea on exertion. The enlargement of the right ventricle begins in the region of the pulmonary conus, and the latter is usually the principal element in the bulging of the left border of the heart known as mitralization. The pulmonary conus is prominent not only because of enlargement but also because of the rotation of the heart to the left and backward due to the enlargement of the right ventricle (page 370). However, prominence of the pulmonary conus is not the only element in mitralization; enlargement of the left auricular appendage and dilatation of the pulmonary artery are usually also concerned, and in some cases the latter is predominant (page 407). Greater enlargement of the right ventricle is characterized by extension of the cardiac shadow not only to the right with increase in the right maximum transverse diameter but also to the left with outward displacement of the apex. When the right auricle becomes dilated, the right border moves still further outward and often is more rounded than usual. It should be remembered that in cases of mitral stenosis with extreme dilatation of the left auricle, this chamber forms a large part of the right border of the heart (page 372).

In some cases of mitral stenosis, the aortic knob is hardly discernible on dorso-ventral illumination. This is due largely to rotation of the heart to the left and backward as a result of enlargement of the right ventricle. But where the stenosis is tight at an early age, the aorta is actually hypoplastic as a result of the small volume of blood that passes through it.

Auscultation.—In the vast majority of instances, the diagnosis of mitral stenosis is established by the characteristic murmurs. In addition, the auscultatory findings may afford valuable information concerning the functional capacity of the heart and the nature of the disturbance in circulatory dynamics.

Rhythm.—Mitral stenosis may run its complete course, including a long period of heart failure, with regular rhythm. In probably a majority of the patients, however, this is not the case. *Auricular*

fibrillation occurs in a higher proportion of cases of mitral stenosis than of any other form of cardiac disease; 50 5 per cent of De Graff and Lingg's[11] patients with mitral stenosis developed auricular fibrillation. The fact that auricular fibrillation is more common when rheumatic heart disease results in mitral stenosis perhaps indicates that the high tension in the left auricle plays some part in the pathogenesis of the arrhythmia Most often, auricular fibrillation in mitral stenosis is continuous from the start; when it is paroxysmal, it usually becomes continuous before long Frequent auricular extrasystoles sometimes portend the onset of auricular fibrillation. Most often, auricular fibrillation—apart from the paroxysmal form which occasionally occurs during acute rheumatic fever—develops only after rheumatic heart disease has been present for many years. The statistics of De Graff and Lingg show that the incidence of auricular fibrillation increases with the duration of rheumatic affliction of the heart, and that, contrary to what has been thought, the arrhythmia occurs with the same frequency in children as in adults who have had heart disease for the same length of time. Sometimes, the patient with mitral stenosis is well compensated until the development of auricular fibrillation, which precipitates heart failure, and may indeed first call his attention to the presence of heart disease In other cases severe heart failure develops while the rhythm is still regular; the addition of auricular fibrillation may then intensify the cardiac insufficiency or exert little apparent influence on the condition of the patient. Despite striking exceptions in which the patient gets along well with digitalis for a decade or more, the advent of fibrillation of the auricles usually ushers in the last phase of rheumatic heart disease. This, as pointed out by De Graff and Lingg, is largely due to the fact that auricular fibrillation generally supervenes only after the rheumatic disease has existed for many years, as they put it, "the die has already been cast before auricular fibrillation sets in." This applies especially to those who must work hard, among persons who can take adequate rest, the likelihood of survival for five, ten or even more years after the onset of auricular fibrillation is not so remote.

Auricular flutter and paroxysmal tachycardia complicate mitral stenosis far less often than does auricular fibrillation.

Auscultatory Findings in Compensated Mitral Stenosis—Most well-compensated patients with mitral stenosis have a murmur that is characteristically low pitched and rumbling, quite closely confined to the vicinity of the apex,* and lasts from shortly after the second sound throughout diastole to terminate with a presystolic accentua-

* The relatively small area over which many loud mitral stenotic murmurs are audible is one of the facts which negate the view, advocated by Cabot[6] that the distance which a murmur is transmitted is purely a function of its loudness

tion in the first sound. If a third sound is audible, it will be noted that the murmur begins with this and not directly after the second sound. Usually, the murmur is better heard with the patient in the reclining position, and generally is more evident when he lies on the left side. Often, the murmur is brought out or accentuated by exercise or the inhalation of amyl nitrite; the shortening of diastole incident to these maneuvers involves corresponding acceleration of blood flow from auricle to ventricle, which apparently favors the production of the murmur by the mitral obstruction. When the heart rate is slow, the murmur may be audible for only a short period following the second sound and in presystole; presumably, the blood current traversing the mitral orifice is sufficiently rapid to produce sonorous vibrations during only these phases of a long diastole and not during the intervening diastasis (page 293) In other cases, only a presystolic murmur is audible, which would seem to indicate that the auriculo-ventricular blood current is rapid enough to produce a murmur only during auricular systole. I have repeatedly, though not invariably, observed that when the murmur of mitral stenosis first appears in a patient who has been followed after acute rheumatic fever, it is confined to presystole at ordinary heart rates. Nevertheless, from such observations one is not justified in concluding that a purely presystolic murmur is indicative of relatively slight obstruction, for it may also occur with tight mitral stenosis The murmur is affected by heart block; when the conduction time is greatly prolonged there may be a perceptible interval between the end of the murmur and the following first sound, while an auricular systole which is not followed by a ventricular contraction may produce an isolated murmur.

The rumbling apical murmur in the middle of diastole or extending up to the first sound with seeming presystolic accentuation has long been regarded as characteristic of mitral stenosis, although it has been recognized that a similar murmur could result from aortic regurgitation (page 478) or from anemia (page 577). Recently, however, Bland, White and Jones[3] found that in 68 patients with mitral diastolic murmurs who succumbed before the age of twenty-one years, 28 revealed at necropsy either no deformity or at most minimal thickening of the free edge of the mitral flaps; in only 2 of these was there sufficient aortic incompetency to suggest the possibility of a Flint murmur. The writer has also repeatedly heard mitral diastolic murmurs within a few months after the onset of apparently initial attacks of rheumatic fever, before sufficient time had elapsed for the development of significant mitral stenosis. Bland and his associates believe that these murmurs result, in some way as yet entirely obscure, from the dilatation of the left ventricle which was present in all their cases. But this scarcely seems compatible with the absence of similar murmurs in the left ventricular dilatation of hypertension and coronary arteriosclerosis. To the writer it would seem more likely, though as yet without proof, that the murmurs may be due to early rheumatic changes in the mitral curtains which diminish their flexibility so that the auriculo-ventricular blood current sets them into audible vibration.

The murmur of mitral stenosis is accompanied by a *thrill* in some three-quarters of the cases Rarely, the thrill is more evident than the murmur and, according to Mackenzie,[32] a slight thrill may precede the murmur by several years as the lesion is evolving. Lichtenstern[25] stated that when the vibration frequency is above 480 per second, the murmur is audible but the thrill not palpable, while when there are less than 16 vibrations per second the reverse is true.

The diastolic murmur terminates abruptly in a characteristically loud and *snappy first sound* It is apparently this sudden termination in a loud sound that creates the usual auditory impression of a crescendo murmur, which is not supported by the phonocardiographic findings The snappy first sound is palpable as an abrupt apical shock. The snappy character of the first sound has been attributed to a rapid systole resulting from the small filling of the left ventricle; Katz and Siegel[21] have shown that in acute experimental mitral stenosis the ejection phase of ventricular systole is actually shortened This conception of the pathogenesis of the snappy first sound is supported by the fact that a similar first sound is often heard in auricular fibrillation when a series of beats follow rapidly on one another, while when the rhythm is slower the first sound is of the usual character. Others attribute the snappy first sound to the tension of the sclerotic mitral flaps.

The first sound is followed in the majority of the cases by a systolic murmur, doubtless most often due to mitral regurgitation. However, a systolic murmur is lacking in many cases in which an enlarged left ventricle points to concomitant mitral regurgitation, or in which the postmortem findings indicate such a mitral leak. Indeed, Coombs[8] states that a systolic murmur was not heard in 46.7 per cent of his cases of mitral stenosis, a percentage which seems higher than my experience.

In faultlessly compensated cases of mitral stenosis, the second sound is natural Accentuation of the pulmonic second sound, which is present in most patients with mitral stenosis, indicates at least slight insufficiency of the left side of the heart (page 510).

In some cases of mitral stenosis, the second sound is followed by a short click, usually best heard a little above and within the apex. Rarely, it is audible in the back. When both the click and the protodiastolic murmur of mitral stenosis are present, careful auscultation reveals that the murmur begins, not immediately after the second sound, but after the click. This click, long ago described by Duroziez[12] and studied in detail by Sansom,[40] has long been familiar to the French, but received little attention in the American literature until the recent excellent study of Margolies and Wolferth.[35] They heard the sound in more than half of their cases of mitral stenosis, and Sansom in over a third of his, but I have not detected

it so often. Margolies and Wolferth's phonocard
show that the extra sound occurs between 0.0
often between 0.06 and 0.11 second after the
second sound. This time relationship accords wi
that the sound is in some way produced by th
sclerotic mitral valve, it has long been known
the *claquement d'ouverture de la mitrale.* Sansom
described cases, especially in children, in which
of the mitral valve was present long before the pr
and other physical signs of mitral stenosis. But
in mind that a loud third heart sound is not rare in
Nevertheless, the development of a third heart s
vidual with a history of rheumatic fever is to be
picious of mitral obstruction.

Effects of Heart Failure on the Auscultatory F
often pronounced. If a patient with mitral steno
first time when in heart failure, it is often impos
the diagnosis until the heart has slowed and c
improved

As has already been mentioned, *accentuation*
second sound is evidence of insufficiency of the left
with resultant engorgement of the lesser circula
raise the tension in the pulmonary artery. Expe
(page 497) indicate that in perfectly compensate
the tension in the pulmonary artery is not increas
pulmonic second sound is not accentuated This
many clinical observations It is true that numer
mitral stenosis and a loud pulmonic second sound
fairly active lives, a state of affairs that may co
but inquiry almost always reveals that the toleran
diminished below the previous capacity. With sev
of the lesser circulation, accentuation of the pulmo
may be so great that it is much the loudest of t
In such cases, the sound is accompanied by a palp
second left interspace. The accentuation of the
sound may lessen when the right ventricle gives
when this is due to auricular fibrillation. But in
pulmonic second sound remains loud despite the
severe systemic venous engorgement. With ter
circulatory failure and consequent diminution in th
to the heart, so often induced in mitral stenosis b
monia, the pulmonic second sound weakens—usual
that the end is near. Accentuation of the pul—

valve preceding that of the aortic because of hypertension of the lesser circulation.

That *auricular fibrillation* modifies the murmur of mitral stenosis was pointed out by Mackenzie,[33] who observed disappearance of the presystolic rumble when this arrhythmia set in. The changes in the stenotic murmur due to auricular fibrillation vary with the ventricular rate. When the ventricular rate is slow, either spontaneously or as a result of digitalization, the murmur is usually confined to the early and middle portions of diastole; the last part of diastole remains clear even though a typical presystolic murmur had been present prior to the onset of fibrillation If the ventricular rate is more rapid, the murmur generally runs up to the first sound, but the presystolic accentuation due to auricular systole is absent. Under such circumstances, the murmur may seem "crescendo" Observations of such a seemingly crescendo murmur in auricular fibrillation has led several clinicians to espouse Brockbank's[5] old theory that the presystolic murmur of mitral stenosis is not really presystolic but early systolic in time and due to regurgitation through the thickened mitral cusps However, the phonocardiographic records of Lewis[28] and others show that the presystolic murmur of mitral stenosis is actually presystolic in time. The reason that the murmur may sound "crescendo" in auricular fibrillation with a rapid ventricular rate, despite the absence of presystolic accentuation due to auricular systole, is that because of the short diastole the murmur lasts right up to the snappy first sound, and this creates the auditory impression of a "crescendo" murmur. By careful auscultation in mitral stenosis with auricular fibrillation, one can often determine that the diastolic murmur seems to be crescendo during a salvo of rapid beats, while when the rate is slower the murmur is confined to the early and middle parts of diastole and is diminuendo rather than crescendo.

When there is auricular fibrillation and heart failure, the murmur of mitral stenosis often loses its characteristic rumbling quality and comes to resemble the murmur of aortic regurgitation This is probably due to lessened velocity of flow through the mitral orifice incident to insufficiency of the left side of the heart With heart failure, the murmur of mitral stenosis may become totally inaudible even though the ventricular rate is not above 100 per minute. Probably every clinician has more than once had the experience, long ago recorded by Hope,[19] of encountering mitral stenosis at necropsy even though he was unable to hear a diastolic murmur or repeated auscultation. I had under my care a man with heart failure in whom the diagnosis of mitral stenosis was established by the demonstration of a very large left auricle, and yet a diastolic murmur could not be made out by a number of competent observers during a period of three weeks. In the latter

part of this period the patient was well enough to be up and about but died suddenly In some cases, the murmur is audible only during a brief period in the middle of diastole. When the left ventricle is very large because of mitral regurgitation or other complication, the diastolic murmur of mitral stenosis may be heard only beyond the left anterior axillary line, I have several times known the diagnosis to be missed because auscultation was not carried out far enough to the left.

Electrocardiographic Findings —These are sometimes instructive, although not uncommonly even tight mitral stenosis is accompanied by a normal electrocardiogram. Sprague and White[44] found definite right axis deviation in 4 of 18 patients with mitral stenosis; in 3 others there was slight right axis deviation; in 10 the electrical axis was unaffected; and in only 1 was there a slight left axis deviation They found the *P* wave prominent in Leads I or II in 6 of the patients. Enlargement of the *P* waves, which is often accompanied by notching, is doubtless to be attributed to the enlargement of the left auricle. That conduction disturbances and various arrhythmias resulting from rheumatic involvement of the myocardium may accompany mitral stenosis goes without saying. The enormous frequency of auricular fibrillation has already been mentioned

Functional Pulmonic Insufficiency in Mitral Stenosis.—Since mitral stenosis is the cause *par excellence* of hypertension of the lesser circulation, the development of functional regurgitation at the pulmonic valve might be anticipated. Actually, Graham Steell[45] long ago described the appearance in patients with mitral stenosis of a diastolic murmur which he termed "the murmur of high pressure in the pulmonary artery," and which has since been known as the Graham Steell murmur. Many clinicians have been skeptical regarding the interpretation of such a murmur, maintaining that it is usually, if not always, due to associated aortic regurgitation Actually, however, it is probably not rare. Cabot[7] encountered the murmur in no less than 20 of 50 patients with mitral stenosis examined at necropsy. Schwartz[42] reports 3 interesting examples, and Scherf[41] encountered 5 instances of the Graham Steell murmur within eight months in cases in which the absence of aortic regurgitation was demonstrated at necropsy. I have several times heard the murmur in cases in which complicating aortic regurgitation was excluded anatomically. The murmur of functional pulmonic insufficiency has also been heard, although very rarely, in conditions other than mitral stenosis which are associated with marked hypertension of the lesser circulation, such as fibroid phthisis, kyphoscoliosis, and sclerosis of the pulmonary arteries. Scherf has also observed the murmur in adhesive pericarditis.

In some cases in which the Graham Steell murmur was present

during life, dilatation of the pulmonic artery and ring was demonstrable at necropsy. In others (such as those of Cabot), this was not feasible, and it is to be presumed that the dilatation of the artery and ring was "dynamic," and akin to the dynamic dilatation of the aorta so often seen fluoroscopically in aortic regurgitation. While the principal cause of the pulmonic dilatation is doubtless the high tension within the vessel, anatomical changes in the wall and ring may also be concerned Kugel and Epstein[24] have demonstrated the striking frequency of inflammatory lesions of the pulmonary artery, especially in the part close to the ring, in patients with rheumatic heart disease Further, long-standing hypertension of the lesser circulation leads to arteriosclerotic changes in the pulmonary artery

The Graham Steell murmur is best heard in the third and fourth left interspaces close to the sternum. It is diastolic in time, almost always soft, and resembles the murmur of aortic insufficiency in pitch and quality. Actually, the Graham Steell murmur can be differentiated from that of an aortic leak only by the absence of the peripheral signs of the latter and by the presence of the manifestations of hypertension of the lesser circulation. The pulmonic second sound is markedly accentuated and accompanied by a diastolic shock. Schwartz has stressed the great dilatation of the pulmonary artery which is often present and readily recognized on roentgen examination There is usually marked enlargement of the right ventricle and auricle When the left ventricle is small, which is the case in those patients in whom stenosis has predominated from early in the disease, the cardiac silhouette is quite characteristic and contrasts diametrically with that in aortic lesions. Pezzi[38] states ample expansile pulsation of the hilus shadows is the rule in functional pulmonic insufficiency, a phenomenon that I have also observed

Scherf has noted distinct improvement in dyspnea and orthopnea when the development of functional pulmonic insufficiency was revealed by the Graham Steell murmur. The phenomenon is readily comprehensible as a consequence of diminution in tension in the pulmonary circuit resulting from the regurgitation into the right ventricle.

Auricular Thrombosis.—The conditions for thrombosis in the left auricle are so favorable in mitral stenosis that it is the rule and not the exception to find antemortem clots in this chamber at necropsy. The principal factor in the formation of the clots is probably stagnation of blood; the severity of the stasis is evident when it is recalled that the capacity of the left auricle in mitral obstruction often exceeds 300 cc., and may surpass 1 liter, while the stroke volume may be less than 30 cc. The small excursion of the wall of a greatly dilated auricle, even when fibrillation is not

present, must also favor the initiation of a clot. Further, inflammatory lesions of the auricular wall are present in most cases (page 493), and they may predispose to local thrombosis as do the similar lesions of the valve curtains.

Thrombi are most common and numerous in the auricular appendage, which is often packed tight with clots and stands out turgidly when the breast plate is removed. The clots take origin in the recesses between the pectinate muscles. Thrombi are also common in the other parts of the left auricle. While most are small, some may reach the size of a cherry or even a plum; occasionally, much larger clots are observed. Flat, stratified clots may line large areas of the auricle with a layer several centimeters thick. A clot may be attached only by a pedicle, and on rare occasions, spherical or ovoid (ball) thrombi are found free in the lumen of the left auricle. Considerable organization of the thrombi is exceptional and calcification a great rarity. In a few cases, Berk[2] and others have detected such calcified auricular thrombi in the roentgen film. The clots may undergo "puriform" softening in the center.

Often enough, thrombi in the left auricle are merely anatomical findings, but in many other cases they play a significant part in the pathogenesis of the clinical picture. This occurs in one of three ways:

1. Detached fragments of clot may embolize to various organs. This occurs most often in the presence of auricular fibrillation, but is by no means rare with regular rhythm. Embolism following the restoration of regular rhythm with quinidine is discussed on page 753. Embolism is more common in patients with heart failure but also occurs in the well-compensated. On rare occasions, symptoms due to embolism usher in the clinical picture in a patient unaware of heart disease. Perhaps the most common of the serious manifestations of embolism in mitral stenosis is hemiplegia; this is more often a right hemiplegia, which may be associated with aphasia. Cerebral embolism may cause sudden death. Occlusion of a peripheral artery may be marked by pain, disability, coldness, and loss of pulsation in the affected extremity; unless the collateral circulation develops sufficiently, gangrene results. Mesenteric, splenic, or renal emboli may be followed by the characteristic symptoms of infarction of the organ in question; I have twice seen infarction of a lobe of the liver in mitral stenosis as a result of embolic occlusion of a primary branch of the hepatic artery. A detached thrombus lodging at the bifurcation of the aorta may lead to pain in the back, paraplegia, and arterial ischemia of the lower extremities with succeeding gangrene; in a case of this type, brought to the hospital in shock so that auscultation was unsatisfactory, the origin of the gangrene in mitral stenosis was not certain until necropsy. Rarely, rather numerous purpuric spots result from small emboli emanating

from the left auricle, although such a picture naturally makes one think first of subacute bacterial endocarditis. Welch[48] has described a case of mitral stenosis in which embolism of the descending branch of the left coronary artery quickly terminated fatally.

2. On extremely rare occasions, either a pedunculated clot or a free ball thrombus partially or almost completely occludes the mitral orifice. This may result in sudden death. Or there may be merely accentuation of dyspnea and other symptoms previously present, so that when the patient succumbs after some days or even a week or two, the obturation of the mitral orifice is a surprise at necropsy. In still other cases, the blocking of the mitral orifice results in a remarkable clinical picture which is sometimes, as in a patient I observed, sufficiently characteristic to permit with considerable probability, though not absolute certainty, the *intra vitam* diagnosis of occluding thrombus. There develops an intense cyanosis and, what is quite characteristic when present, an almost cadaveric coldness of the four extremities, the tip of the nose, and the ears, which may go on to gangrene in some or all of these parts. The arterial pulsations are very feeble or absent in all the extremities. Diagnosis is only feasible with much probability in the extremely rare cases in which such symmetrical ischemia of all the extremities, the tip of the nose, and the ears develops. And even with this picture, I once encountered at necropsy only a remarkably tight mitral stenosis without occlusive thrombosis In those cases in which ischemia and gangrene of only the lower extremities is present, the condition can hardly be differentiated from embolism at the bifurcation of the aorta. Cerebral symptoms may occur from ischemia of the brain. In a few instances, as in one of the cases of Schwartz and Billoon,[43] there has been intermittent obturation of the mitral orifice by a ball thrombus, with corresponding intermittency of the symptoms.

The pathogenesis of this remarkable symmetrical ischemic gangrene of the extremities in mitral stenosis is discussed on page 656, it appears to be due to intense peripheral vasoconstriction

Pulse and Blood Pressure.—Changes in rate and rhythm have already been discussed. In well-compensated cases of mitral stenosis, the pulse is often normal. In other instances, even though heart failure is insufficient to prevent the patient from attending school or an occupation, and despite normal or even high blood pressure, the pulse is small in volume. The pulse is apt to be especially small in "pure" stenosis with a small left ventricle.

The arterial pressure is likewise within normal limits in patients with uncomplicated and well-compensated mitral stenosis. This state of affairs may continue after the onset of heart failure. But in other cases the latter has some, though rarely a pronounced, effect on the arterial tension. Sometimes, the systolic and pulse

pressures fall slightly. More often, the onset of heart failure in mitral stenosis is accompanied by a rise in the diastolic pressure, with a smaller increase in systolic pressure (page 81). With restoration of compensation by digitalization or other means, the pressure falls to its former level These changes rarely exceed 10 or 20 mm. of mercury. Since there can be little doubt that the cardiac output is decreased in these cases with tight mitral obstruction and heart failure, it would seem that the maintenance or elevation of the arterial pressure is to be attributed to vasoconstriction. The latter doubtless contributes to the notable coldness of the extremities in some patients with mitral stenosis whose exercise tolerance is fairly good

A remarkable phenomenon is the high incidence of *essential hypertension* in middle-aged individuals, especially women, with mitral stenosis Boas and Fineberg[4] found high blood pressure in 39 of 158 persons with mitral stenosis, and Levine and Fulton[26] in no less than 58 per cent of cases of mitral stenosis over forty-five years of age Young patients with mitral stenosis do not have high blood pressure, apart from the rare complication of glomerulo-nephritis, but the incidence of hypertension in the middle aged with mitral stenosis is far too high to be purely accidental. One hypothetical possibility is that the vasoconstriction mentioned in the preceding paragraph as occurring in mitral stenosis may bring out the elevation in blood pressure in an individual with the hereditary, constitutional predisposition which apparently lies at the root of all essential hypertension

Systemic Venous Engorgement in Mitral Stenosis.—Only a minority of patients with mitral stenosis succumb while well compensated as a result of intercurrent disease or an embolus from the left auricle, or during the stage of isolated insufficiency of the left heart as a result of such complications of pulmonary engorgement as bronchopneumonia, pulmonary infarction, or edema of the lungs The large majority sooner or later develop insufficiency of the right side of the heart, with systemic venous engorgement The cervical veins become distended, the venous pressure rises, the liver swells, and dependent edema and transudates in the serous cavities develop These phenomena do not differ from those of other forms of right ventricular failure, and have been described in detail in other chapters of this book. Here it may be mentioned that, especially when it is precipitated by auricular fibrillation, the right ventricular failure of mitral stenosis is peculiarly amenable to improvement under rational treatment. There are many patients with mitral stenosis who have five or more bouts of severe right ventricular failure at considerable intervals, even several years, and between them are able to follow an occupation. Among the patterns of

right ventricular failure in mitral stenosis, attention should perhaps be called to one, not very common, in which there is large, hard swelling of the liver and recurrent ascites, so that the picture simulates constrictive pericarditis or even Laennec's cirrhosis of the liver. It may also be mentioned that the conditions for the development of cardiac icterus are especially favorable in mitral stenosis with severe heart failure because of the frequent coincidence of multiple pulmonary infarctions and engorgement of the liver.

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CHAPTER XXVIII

HEART FAILURE INITIATED BY INSUFFICIENCY OF THE RIGHT SIDE OF THE HEART

FAILURE of the right side of the heart occurs in three general categories of cases:

1. By far the most common is that in which the right-sided failure is secondary to antecedent insufficiency of the left heart in hypertension, arteriosclerotic disease of the left ventricle, or aortic or mitral valvular defects. The left-sided failure results in hypertension of the lesser circulation and sometimes bulging of the interventricular septum to the right (page 447). Through these mechanisms, usually acting in combination with diseases of the muscle of the right ventricle which impairs the functional efficiency of this chamber, insufficiency of the right side of the heart sooner or later complicates most instances of primary left-sided failure.

2. Right- and left-sided failure may evolve coincidently from causes which increase the work of the whole heart—notably hyperthyroidism—or impair the functional capacity of the myocardium of both sides of the heart—for example, rheumatic, diphtheritic, and arteriosclerotic disease of the heart muscle, although the last named more often affects the left ventricle primarily. When both halves of the heart are affected simultaneously and equally, symptoms of right-sided failure tend to predominate, because the weakening of the right ventricle may diminish its output and thus lessen the work of the left ventricle.

3. Primary right-sided failure is much less common than solitary insufficiency of the left side of the heart. The former occurs most often as a result of diseases of the lungs or their vessels which increase the resistance to blood flow through the pulmonary circuit. Among the causes of such increase in resistance in the pulmonary circuit and resultant *cor pulmonum*, as it has been called, are the following. Emphysema, fibroid phthisis, pneumokoniosis and other non-tuberculous cirrhoses of the lung, extensive pleural adhesions, kyphoscoliosis and other thoracic deformities, and certain rare diseases of the pulmonary arteries. Acute right-sided failure may be caused by pulmonary embolism or pneumonia. Finally, primary right-sided failure arises from the relatively rare organic defects of the pulmonic and tricuspid valves and from congenital lesions with a shunt between the two circulations.

CLINICAL PICTURE OF FAILURE OF THE RIGHT SIDE OF THE HEART

Right ventricular failure results in two general varieties of symptomatology, depending on whether the onset of severe failure is gradual or abrupt:

(1) *Chronic right ventricular failure: The clinical picture of failure of the right side of the heart is dominated by the symptoms and signs engendered by engorgement of the venæ cavæ and their tributaries.* Characteristic of pure right-sided failure, a relatively uncommon disturbance, is that the systemic venous engorgement is not accompanied by pulmonary congestion. On the other hand, if the right-sided insufficiency is secondary to weakness of the left heart, a much more frequent state of affairs, the manifestations of pulmonary engorgement are also present. When right-sided failure results from pulmonary disease, the consequences of heart failure are commingled with those due to impairment of external respiration by the lesions in the lung

An obvious and diagnostically important characteristic of the venous engorgement of right heart failure is that it implicates the territories of both the superior and the inferior vena cava, although it may be more pronounced in either. If venous engorgement is severe in the tributaries of one of these veins and absent in the other, one should always be suspicious of some extracardiac venous obstruction.

(2) *Acute right ventricular failure* occurs classically in massive pulmonary embolism and very rarely in pneumonia. The clinical picture is that of shock due to the abrupt fall in cardiac output with which are associated the consequences of engorgement of the systemic veins.

The principal manifestations of right-sided failure are the following (for details regarding each, the reader is referred to the chapters on the individual symptoms and signs):

1. *Cyanosis.*—This is present in the large majority of instances of right heart failure, although there are patients with swollen veins and liver in whom cyanosis is not evident on inspection. The cyanosis of right heart failure is due to distention of the venules and venous capillaries as well as to increased oxygen loss in the capillaries resulting from retardation of blood flow. Apart from certain cases with congenital heart disease in whom cyanosis is due principally to causes other than heart failure, the most intense cyanosis is seen when the cardiac insufficiency is secondary to a pulmonary lesion which interferes *per se* with the gas exchange. In these cases, impaired oxygenation in the lungs is added to the aforementioned peripheral mechanisms of cyanosis. In a general way it may be said that in right heart failure cyanosis predominates over dyspnea.

the reverse of what happens in left-sided failure; to a large extent, this is due to the fact that right-sided failure is generally associated with lesions of the lungs and pulmonary vessels.

2. *Engorgement of the Superficial Veins.*—Repletion of the cervical veins is almost always obvious in severe right heart failure. There may also be prominent pulsation of these veins and, what is characteristic when present, the ventricular form of the venous pulse. However, in slight or even moderate failure of the right ventricle, the fulness of the cervical veins may not be evident on inspection, especially if the individual is obese or the veins deeply situated. Then the engorgement of the veins may be rendered evident by pressure on the right upper quadrant In exceptional instances of extreme right heart failure with the clinical picture of cardiac shock, the veins of the neck are distended while those of the extremities are almost devoid of blood (*cf* page 656).

3. *Increase in Venous Pressure.*—This serves as a quasi-quantitative measure of the severity of failure of the right heart But the parallelism is no more than a general one, for the venous tension is also affected by the circulating blood volume and other variables Moreover, in relatively slight right ventricular failure, already documented by swelling of the liver, the venous pressure may not be definitely above the upper limits of normal by our relatively coarse clinical methods of measurement, the engorgement merely serving to fill out veins that were not before fully distended (page 110). In such cases, a marked rise in venous pressure on compression of the right upper quadrant may reveal the engorgement of the veins (page 256).

4. *Swelling and Tenderness of the Liver.*—This is a valuable sign of insufficiency of the right side of the heart, which is rarely absent, and the fluctuations of which often mirror the functional accomplishment of the right ventricle. In long-standing right ventricular failure, the liver may shrink as a result of fibrotic changes although the venous pressure remains high. In severe right-sided failure, expansile hepatic pulsation may be present, but it should be remembered that hypertrophy of the right ventricle without notable failure produces transmitted pulsation of the liver. Cardiac icterus may occur in uncomplicated right-sided failure, but is less common than in combined right- and left-sided failure, where the factors of pulmonary infarction and hepatic engorgement supplement one another.

Rarely, the *spleen* is palpably enlarged as a result of right heart failure.

5. *Subcutaneous edema* and transudation into the serous cavities are classical manifestations of right heart failure. But they are not always present, even when venous pressure is very high, because of the important rôle of accessory factors (Chapter XII) in the

pathogenesis of cardiac dropsy. Absence of edema despite high venous pressure is especially common when the patient is in bed and under treatment, for edema is the symptom of heart failure against which therapeutic measures are most effective.

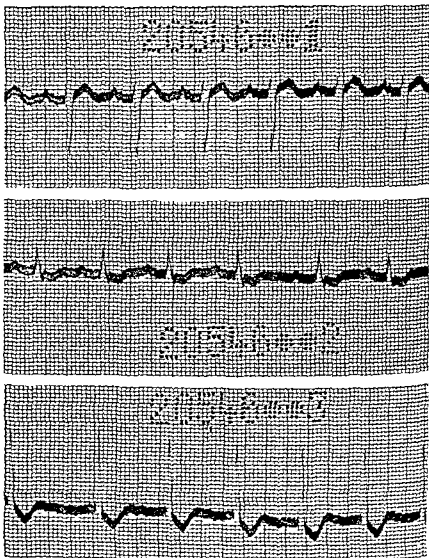


FIG 20 —Electrocardiogram of a patient with pronounced hypertrophy and dilatation of the right ventricle The voltage of the *Q–R–S* complex is high, rotation of the electrical axis to the right is revealed by the downward direction of the major deflection of this complex in the first lead and the upward direction in the third lead Inversion of the *T* wave in the second and third leads is the rule in right ventricular preponderance

6. The *right ventricle and auricle* are hypertrophied and dilated. Evidences of relative tricuspid regurgitation may be present, and on rare occasions right-sided gallop rhythm is heard A previously accentuated pulmonic second sound may become weaker when the right ventricle fails. The electrocardiogram sometimes, but not always, exhibits rotation of the electrical axis to the right (Fig 20).

7 *The lungs are not engorged in uncomplicated right-sided failure*, and indeed decreased density of the lung fields in the roentgenogram may afford evidence of subnormal blood content

8 The *arterial pressure* is not characteristically affected. Usually, it is little changed until the terminal fall I have several times seen considerable elevation of the arterial pressure during right heart failure secondary to chronic pulmonary disease

9. *Oliguria* is a cardinal manifestation of systemic venous stasis. The urinary volume is a valuable index of the progress of right sided failure. The urine presents the usual "cardiac" characteristics and may be albuminous.

10. The *cerebrospinal pressure* is elevated as a result of the rise in venous pressure

11. *Dyspnea* is almost always present in right-sided failure, but its intensity varies greatly While the dyspnea of patients with right heart failure secondary to emphysema or other pulmonary disease may be agonizing, in the rare primary right-sided failure of tricuspid or pulmonic valvular disease there may be but little dyspnea. The frequent alleviation of dyspnea when right ventricular failure complicates insufficiency of the left heart has already been mentioned. There are many patients, in whom bulging veins and a swollen liver attest to severe right ventricular failure, who do not complain of dyspnea at rest. *Orthopnea* is often absent in right-sided failure.

PULMONARY EMPHYSEMA

Among the clinical pictures commonly confronting the practitioner is that in which an individual with an emphysematous thorax complains of dyspnea and cough. From a therapeutic point of view, it is most important to determine to what extent the dyspnea, cyanosis, and other symptoms are attributable to the pulmonary lesions *per se*, and how far they are the result of circulatory failure. This is often a difficult problem. Indeed, experienced clinicians differ greatly as to how often emphysema leads to heart failure. Thus, while Romberg[59] considered heart failure secondary to emphysema as common, and White and Jones[72] observed 21 cases of "pulmonary heart disease" among 2314 patients with organic cardiac disease, Kountz[37] and Hurtado[31] and their respective co-workers reported considerable series of patients with emphysema

in whom heart failure was very infrequent. More recently, however, Kountz, Alexander and Prinzmetal[38] have published necropsy observations showing that the heart is affected in the majority of patients with emphysema. Parkinson and Hoyle[61] found cardiac failure secondary to emphysema alone to be rare, of late occurrence, and almost always terminal. In New York City, especially in elderly workers in dusty trades, I have observed many cases which I considered as "emphysema heart," *i. e.*, heart failure in the pathogenesis of which emphysema played at least an important rôle. Nevertheless, it would appear that, as brought out especially by Kountz and his co-workers, symptoms due directly to emphysema have often been attributed to heart failure. For this reason, we will first discuss certain of the manifestations of emphysema which may be confused with those of heart failure.

The Forms of Emphysema.—Under the generic designation of emphysema are included several pathogenetically distinct conditions, and not all of them impede the ventilation and circulation of the blood. In those cases in which functional disability of one or more lobes (*e. g.*, in fibroid phthisis) is followed by the distention of other lobes, or where pulmonary distention results from residence at high altitudes, it is to be presumed that the enlargement of the lungs subserves a compensatory function and facilitates the ventilation of the blood. Apart from these compensatory forms, two main varieties of emphysema may be differentiated:

1 *Non-obstructive Emphysema.*—This type occurs almost always in the aged, and while the thorax is hyperresonant and may be barrel-shaped, the lungs are little increased in volume and may even be small (senile or small-lunged emphysema) When the chest is opened, the lungs collapse quite rapidly This form of emphysema is not due to asthma or other bronchial obstruction It has been considered as due to senile atrophy of the interalveolar septa. While this may be true to some extent, Freund[23] long ago enunciated the view that this form of emphysema is primarily a disease of the thoracic skeleton and the pulmonary changes are secondary. This conception has been adopted, in another form, by Loeschke[45] and Kountz and Alexander.[36] The latter investigators believe that the underlying lesion is a degenerative process in the intervertebral disks, as a result of which the dorsal spine is first straightened out and later kyphotic; the consequent alterations in the form of the thorax entail a change in the position of the lungs and the forces acting upon them, with ultimate alveolar distention and loss of elasticity.

Available evidence indicates that this non-obstructive form of emphysema is but slightly deleterious to respiration and circulation. According to Kountz and Alexander, the vital capacity is little diminished and the oxygen saturation and carbon dioxide content of the arterial blood normal In one such case, Hurtado and his associates found the residual air normal. Kountz and Alexander observed that in non-obstructive emphysema, in contrast to the obstructive form, the excursion of the diaphragm is ample and may even be unusually great; respiration is largely abdominal. I have repeatedly observed at the necropsy of individuals with non-obstructive emphysema that the heart was small and the seat of brown atrophy, with no indication that it had been subjected to unusual strain. When heart failure develops in the presence of non-obstructive emphysema, it is not secondary to the pulmonary changes, almost always, the cardiac disease is

due to coronary sclerosis or hypertension. Non-obstructive emphysema thus appears to be of little clinical significance

2 *Obstructive Emphysema.*—This results from bronchial obstruction, most often asthma or chronic bronchitis. In the past, there has been much dispute whether it is the increased resistance to inspiration or to expiration which leads to emphysema The recent investigations of Prinzmetal[16] indicate that immoderate inspiratory distention of the lung during the asthmatic paroxysm is probably the primary factor He found in 4 humans during attacks of bronchial asthma, as well as in animals with experimental bronchoconstriction, that *intrapleural pressure was more negative* than between the paroxysms The more negative intrapleural pressure results in distention of the lungs, which when repeated often enough leads to diminution in their elasticity and emphysema. A similar mechanism doubtless operates when the bronchi are narrowed by the inflammatory changes of bronchitis In patients with severe and protracted cough, an expiratory factor probably also enters into the production of emphysema of the apices and margins of the lungs, which become distended during the powerful expiration of cough

In obstructive emphysema the lungs are large and collapse little when the chest is opened This is the clinically important variety of emphysema, the one which leads to severe disturbances in ventilation and sometimes in circulation, and is the one to which the remainder of this section will be confined.

Pseudocardiac Symptoms in Emphysema.—Emphysema may produce a galaxy of symptoms—dyspnea, cyanosis, swelling of the superficial veins, and rarely edema—which simulate heart failure, and in the past have often been confused with the latter Evidence that these symptoms are not necessarily due to cardiac failure is afforded by their frequent existence for years in the absence of enlargement of any of the cardiac chambers, an invariable accompaniment of protracted heart failure. Moreover, they may occur with normal circulation time With the radium C method, Weiss and Blumgart[59] observed normal arm-to-arm circulation time in moderate emphysema, although there was some prolongation in advanced cases. Using decholin for measuring the arm-to-tongue circulation time, Tarr, Sager and Oppenheimer[65] observed normal values in emphysema. With saccharin, Hitzig, King and I have repeatedly found the arm-to-tongue circulation time within normal limits in emphysematous patients who were cyanotic, dyspneic on trivial exertion, and had slight elevation of venous pressure. Measurement of the circulation time is a valuable clinical aid in determining whether or not emphysema is complicated by circulatory failure.

Dyspnea —There are patients with marked emphysema, which has produced considerable cyanosis, who do not complain of dyspnea, and are capable of hard work. But sooner or later, most emphysematous individuals become short of breath. The dyspnea of emphysema is exertional; paroxysmal dyspnea in a patient with

emphysema is usually to be attributed to underlying bronchial asthma and can most often be relieved promptly by epinephrin.

Pathogenesis.—It has long been realized the elasticity of the lungs is diminished in emphysema. This conception has been supported by measurements of the elasticity of pulmonary tissue at postmortem. Recently, Christie[13] has shown *in vivo*, by simultaneous tracings of the volume of tidal air and intrapleural pressure, that the loss of pulmonary elasticity in emphysema may be almost complete. Among the consequences of diminished pulmonary elasticity are the following:

1. The lessened elastic pull of the lungs on the chest wall results in displacement of the latter toward the inspiratory position. In consequence, inspiration is started with the chest already in such a position that further excursion is limited and takes place at a mechanical disadvantage. The low position of the diaphragm at the start of inspiration is especially disadvantageous. A further result is that the air drawn in at each inspiration is diluted by the abnormally great volume of air already present in the lungs.

2. In health, expiration is largely a passive process, in which the elastic recoil of the lung is an important factor. To the extent that pulmonary elasticity is diminished, active muscular work must be substituted in expiration

3 Christie points out that the diminished elasticity of the lung in emphysema results in unequal ventilation, the forces of respiration acting much more powerfully on the superficial portions of the lung than on those more deeply situated. Such unequal ventilation obviously diminishes the efficiency of respiration.

In most, if not all, cases of obstructive emphysema, the inflammatory or spastic narrowing of the bronchi which originally produced the emphysema doubtless contributes substantially to the mechanical impairment of respiration. Bronchoscopy often reveals considerable amounts of mucoid secretion in the large bronchi of emphysematous individuals Intensification of dyspnea is the rule during exacerbations of bronchitis. And Jagic and Spengler[32] have found that the injection of epinephrin increases the vital capacity in emphysema

The mechanical impairment of respiration in emphysema is attested quantitatively by the following characteristic pattern of the respiratory volumes (for details, see Hurtado[31] *et al.*):

1. The lung volume (total capacity) is little changed.

2. The mid-capacity is increased, an expression of the above-mentioned displacement of the lungs toward the inspiratory position.

3. The vital capacity is decreased. The diminution in vital capacity serves as a crude, but useful, clinical measurement of the impairment of respiration, for Hurtado and his associates found that it parallels roughly the severity of the dyspnea. In their

cases with very severe dyspnea, it averaged 60 9 per cent below normal. According to these investigators, the decrease in vital capacity is more at the expense of the complementary than of the reserve air.

4. The residual air is increased, averaging 2 84 liters in the patients of Hurtado *et al.*, as contrasted with their normal average of 1.36 liters.

5. The minute volume of respiration is increased Staehelin and Schutze[84] found an average of 11 8 liters as contrasted with a normal of 7.6 liters. Inasmuch as the oxygen consumption is normal, this is an indication of the lessened efficiency of ventilation

These disadvantageous changes in the mechanics of respiration are doubtless the principal causes of the defective aeration of the blood which is demonstrable (see next paragraph) in emphysematous subjects with notable dyspnea Accessory factors may, however, also be concerned Christie points out that in emphysema the alveoli at the periphery of the lung are overdistended and have a very sparse blood supply, with the result that their ventilation is largely wasted This is the more important because in severe emphysema the total surface area of the alveoli available for ventilation is greatly diminished. The possibility that changes in the walls of the alveoli may interfere with gas exchange has been suggested but not substantiated; on the contrary, Krogh[40] found normal alveolar permeability in 3 patients with emphysema

The deficient aeration of the blood in emphysema is revealed by decrease in the arterial oxygen saturation, and sometimes also by retention of carbon dioxide In 20 of the 24 patients with pulmonary emphysema studied by Hurtado, Kaltreider and McCann,[82] the oxygen saturation of the arterial blood was below 94 per cent, their lower limit of normal The degree of oxygen saturation was correlated with the abnormalities in pulmonary capacity Much more severe impairment of respiratory mechanics appears to be necessary to cause carbon dioxide retention than deficient oxygenation of the arterial blood Hurtado, Kaltreider and McCann found abnormally high carbon dioxide content of the arterial blood in only 3 of their 24 cases of emphysema. Scott[61] long ago showed that carbon dioxide retention in emphysema may be accompanied by increase in alkali reserve, presumably a compensatory mechanism

From these findings, it would appear that arterial anoxemia is a far more important factor in the pathogenesis of dyspnea in emphysema than in heart failure. However, it develops so gradually that the patient often accommodates himself surprisingly well to low oxygen saturation of the arterial blood, one often observes well-marked cyanosis in emphysematous subjects who have considerable exercise tolerance In the past, it has been thought that, akin to what happens in high altitudes, an important mechanism in adapta-

tion to the defective ventilation of emphysema is increase in circulating blood volume and polycythemia. Plesch[52] and Uhlenbruck[53] and Vogels observed increased circulating blood volume in emphysema. Price-Jones[54] found that the mean diameter of the red cells is increased in emphysema, and while Lemon[41] did not observe this augmentation in corpuscular volume, he found an increase of 20 per cent in corpuscular hemoglobin. On the other hand, the recent detailed studies of Kaltreider, Hurtado and Brooks[34] disclosed no significant variations from normal in circulating plasma or cell volume, or in the total quantity of hemoglobin in circulation. Nor did they find any relationship between circulating blood volume and changes in pulmonary capacity. On the other hand, I have several times observed definite polycythemia and increase in circulating blood volume in individuals with long-standing emphysema, so it may be that exceptionally the bone marrow is stimulated by the protracted anoxemia, and that the resultant increase in circulating hemoglobin subserves a compensatory function.

Cyanosis is present in the large majority of individuals with marked emphysema It has already been mentioned that there may be severe cyanosis with comparatively little dyspnea The cyanosis is due to arterial anoxemia, the causation of which has already been discussed That the cyanosis is due to pulmonary causes and not to slowing of blood flow in the periphery is often indicated by the warmth of the bluish finger tips. Emphysematous patients with cyanosis generally develop clubbing of the fingers, though this rarely reaches a severe degree unless there is also bronchiectasis

Engorgement of the Systemic Veins.—The first glance at a patient with long-standing emphysema not uncommonly reveals bulging cervical veins, which also often appear to be of larger caliber than normal. Pulsation is not prominent in these veins and may not be discernible, the ventricular form of the venous pulse is absent. During asthmatic paroxysms, the engorgement of the cervical veins becomes more marked. That this venous engorgement is not due to cardiac failure is indicated by the fluoroscopic finding that the heart is not enlarged; the only form of cardiac failure which presents the combination of a small heart and engorged cervical veins is that present in constrictive pericarditis.

Measurement of the venous pressure in patients with emphysema and distended cervical veins generally does not reveal as much elevation as one might anticipate from inspection of the veins Kountz[39] and his associates found that in emphysema the venous pressure is elevated in rough proportion to the degree of bronchial obstruction. They observe that the rise in venous pressure induced by an asthmatic paroxysm disappears immediately after the attack when there is little emphysema, but when the attack occurs in a

patient with severe emphysema the venous pressure drops much more slowly and may take several days to fall within the normal range. I have also seen persistent elevation of venous pressure to 12 or 14 cm of water in several patients with emphysema but without heart failure. But there are also many such patients, a decided majority in my experience, in whom the venous pressure was less than 8 cm of water and therefore within the limits of normal. Weiss and Blumgart[69] also found the venous pressure normal in most cases of emphysema. The venous pressure is often normal in emphysematous subjects with bulging and seemingly engorged cervical veins, the prominence of these vessels may be due to thickening of the wall and dilatation which is probably a heritage from repeated engorgement during paroxysms of asthma or bronchitic cough.

Kountz and his associates have adduced evidence that venous engorgement in emphysema without heart failure is due to elevation in intrapleural pressure They have observed that in severe obstructive emphysema the intrapleural pressure is less negative than the normal figures of about −4 cm of water during expiration and −8 cm. during inspiration Von Neergaard and Wirz[67] also found that the average intrapleural pressure in emphysema is −3.2 cm of water as contrasted with the normal figure of −5 7 cm. Often patients with severe emphysema have an intrapleural pressure which is close to atmospheric and in severe cases may reach +5 cm of water or more during ordinary expiration Elevation of intrapleural pressure increases the resistance to the venous return to the heart and thus elevates the venous pressure. Kountz and his associates found that in patients with emphysema and asthma, variations in intrapleural pressure are reflected in corresponding changes in venous pressure. And when they produced emphysema in dogs by partially obstructing expiration, they observed parallel variations in intrapleural and venous pressures Another cause for venous obstruction has been described by Eppinger and Hofbauer,[18] who found that the low position of the diaphragm entails compression of the inferior vena cava as it passes through the foramen quadrilaterium

Kountz and his co-workers believe that dependent *edema* in patients with emphysema is not necessarily due to heart failure, but may result directly *from the emphysema through the intermediacy* of the elevation in venous pressure and anoxemic increase in permeability of the capillaries. The low position of the diaphragm occasionally renders the liver palpable in the absence of heart failure

Cough is rarely lacking in emphysema It is generally due to the bronchitis or asthma which produces the emphysema, and antedates the latter.

Causes of Right Ventricular Strain in Emphysema.—The work of the right ventricle is augmented in severe emphysema as a result of increased resistance to blood flow through the lungs, which elevates the pressure in the pulmonary artery. The evidences of increased tension in the pulmonary artery are as follows:

1. In many cases of emphysema, the pulmonic second sound is louder than the aortic second sound. The difference is generally quite clear even though all the sounds are distant as a result of the distention of the lungs. In some instances in which the accentuation of the pulmonic second sound is not evident, this is due to coincident accentuation and ringing quality of the aortic second sound resulting from systemic hypertension or elongation of an arteriosclerotic aorta with approximation to the chest wall.

2. At necropsy, one often finds marked arteriosclerosis and arteriolosclerosis of the pulmonary radicals, a lesion which there is every reason to attribute to long-standing hypertension.

3. Most important of all is the frequent finding at necropsy of hypertrophy of the right ventricle. While Kountz and his associates originally found little evidence of right ventricular hypertrophy in emphysema, Kountz, Alexander and Prinzmetal[33] later described dilatation and hypertrophy of the right ventricle in the majority of their cases. The occurrence of hypertrophy of the right ventricle in emphysema has been established by many pathological anatomists. Loeschke,[34] who studied the pathological anatomy of emphysema in great detail for many years, states that the right ventricle is hypertrophied when emphysema is widespread throughout both lungs, and that the hypertrophy is especially great when there are extensive areas of atelectasis due to bronchial obstruction. Kirch[35] has carried out careful studies on the size of the chambers of the heart and weighed them by the method of Mueller, he found hypertrophy of the right ventricle up to triple the normal. I have often seen hypertrophy of the right ventricle at necropsy for which no cause was evident other than increase in resistance to blood flow through the lungs resulting from emphysema. Dr. Paul Klemperer tells me he has made many similar observations. In some of the cases with right ventricular hypertrophy, the left side of the heart was not enlarged. Often, however, the left ventricle is also hypertrophied, which is often, but not always, a result of accompanying systemic hypertension. Hypertrophy and dilatation of the left ventricle may perhaps also result from protracted anoxemia (page 538).

In a majority of dogs in which they produced emphysema, Kountz, Alexander and Prinzmetal[33] found hypertrophy of the right and left ventricles.

The demonstration of right ventricular hypertrophy *in vivo* in emphysema is often not feasible. As already mentioned, hyper-

trophy with little dilatation causes but slight enlargement And in emphysema the low level of the diaphragm causes the heart to assume a median position and rotate so that the transverse diameter is smaller than normal. I have repeatedly seen hypertrophy of the right ventricle at necropsy in cases in which the transverse diameter of the heart in the roentgen-ray was small In a careful radiologic study of 80 patients with emphysema, Parkinson and Hoyle[61] were able to demonstrate enlargement of the right ventricle in 18, the right auricle in 11, the pulmonary conus in 33, and the pulmonary artery in 22 cases. In elderly subjects the emphysematous heart may assume a more transverse position as a result of elongation of the arteriosclerotic aorta.

We may now turn to the causes of the right ventricular hypertrophy in emphysema Three main factors operate to increase the resistance to blood flow through the lungs and thus augment the work of the right ventricle

1. The widespread destruction of interalveolar septa entails obliteration and disappearance of capillaries So many capillaries may be obliterated that new arteriovenous anastomoses are formed (Rindfleisch[56]) The result of the capillary obliteration is that the total cross-section of the pulmonary vascular bed is diminished In order that the volume flow be maintained, despite the smaller cross-section of the stream bed, the pressure in the pulmonary artery must rise, which can be accomplished only by increased work of the right ventricle That maintenance of volume flow through such increase in pressure actually occurs was demonstrated long ago by Lichtheim[42] He found that when the left pulmonary artery is occluded, the volume of flow is maintained, but this is achieved by an increase in pressure in the right pulmonary artery from its previous value of 180 mm of water to 260 mm

2. Most patients with severe emphysema have a history of many years of cough and asthma, or both During cough or an asthmatic paroxysm, the intra-alveolar pressure during expiration rises to high levels, Staehelin[63] estimates that it may exceed 50 mm. of mercury The elevation of pressure within the alveoli during cough or an asthmatic paroxysm compresses the minute vessels of the lung and thus augments the work of the right heart Hypertrophy of the right ventricle due to this cause has been observed in whooping cough, and it is probably an important factor in emphysema.

3. The influence of the respiratory position on blood flow through the lungs requires further investigation. However, the detailed studies of Cloetta[14] indicate that while the minute vessels of the lung are distended by axial traction early in inspiration, at the height of deep inspiration they are compressed It is therefore quite probable that the marked displacement of the chest toward the inspiratory

position in emphysema serves to augment the resistance to blood flow through the lungs.

Kountz and his associates point out that the obstruction to venous return by the increased intrapleural pressure in emphysema tends to spare the right heart. However, the fact that the right ventricle is hypertrophic in many cases of severe emphysema indicates, at least in these instances, that the factor of increased resistance in the pulmonic vessels is preponderant.

Heart Failure in Emphysema.—The hypertrophied right ventricle usually is able to master the increased pulmonary resistance for years or decades, and many patients with severe emphysema never develop heart failure, succumbing to bronchopneumonia or an independent ailment. But in other cases the right ventricle ultimately gives way with the appearance of signs of systemic venous engorgement exceeding those due to heightened intrapleural pressure

Often, the precipitating cause of the failure of the right ventricle is not evident. In many cases, necropsy reveals well-marked coronary arteriosclerosis Cardiac insufficiency may then be due to the combination of increased work of the right ventricle as a result of the pulmonary changes and inability to increase correspondingly the blood supply because of the coronary disease. It is true that gross myocardial infarction practically always affects the left ventricle primarily, but there can be no doubt that with marked arteriosclerosis of both coronaries the blood supply of the right ventricle must suffer, a conception that is supported by the frequent finding of interstitial fibrosis. In other cases, heart failure follows bronchopneumonia, and it is possible, though hard to prove, that what is so glibly called toxic damage to the myocardium is damage by anoxemia. This suggestion seems very plausible, for anoxemia may be present for years and the myocardium requires an abundant supply of oxygen. It has repeatedly been shown experimentally that anoxemia leads to cardiac dilatation. As suggested by Hoover,[23] anoxemic damage to the myocardium might account for the fact that the left ventricle is frequently also found dilated in emphysema Since all forms of dilatation tend to be replaced by hypertrophy (page 310), it is not surprising that the left ventricle is also sometimes found hypertrophic. Moreover, anoxemia tends to increase the cardiac output, and would thus favor dilatation and hypertrophy of the heart through the intermediacy of augmented work. But it should be remembered that systemic hypertension is a common accompaniment of emphysema and, as emphasized by Parkinson and Hoyle, doubtless is the most common cause of left ventricular enlargement in emphysematous subjects.

The manifestations of right ventricular failure are the usual ones and are superadded to the pre-existent symptoms of emphysema. Dyspnea becomes more severe, the systemic veins are more engorged

and pulsate, the liver is enlarged and tender, and dependent edema appears. Ascites occasionally develops but hydrothorax has, in in my experience, been rare in the heart failure of emphysema. Cyanosis is usually very pronounced because of the combination of circulatory and ventilatory insufficiency; some of the patients ultimately resemble the "black cardiacs" (page 544) The heart is rapid. Auricular fibrillation is not rare. The demonstration of cardiac enlargement by palpation or percussion is usually not feasible because the voluminous lungs obscure the cardiac dulness. Roentgen examination often reveals enlargement of the right ventricle and auricle and pulmonary artery (page 537), with which may be associated, for reasons already mentioned, enlargement of the left side of the heart. However, sometimes it is difficult to demonstrate cardiac enlargement actually present because this is masked by the median position of the heart due to the low diaphragm. Epigastric pulsation is common but has not its usual value as a sign of right ventricular hypertrophy because of the low position of the diaphragm. Right-sided gallop rhythm in the xiphoid region is a rare finding. One would anticipate right axis deviation in the electrocardiogram, but it is present in only a minority of the cases The blood pressure is usually maintained until close to the end and may even rise, presumably as a result of defective aëration of the blood Some of the patients go through several bouts of heart failure over a period of years, rallying with appropriate treatment. But other cases go steadily downhill.

FIBROID PHTHISIS, NON-TUBERCULOUS FIBROSIS OF THE LUNGS AND ADHESIVE PLEURISY

Hypertrophy of the right ventricle is not uncommonly found at the necropsy of individuals who have succumbed to fibroid phthisis or widespread cirrhosis of the lungs secondary to pneumokoniosis or chronic non-tuberculous infections of the lungs and bronchi. Coggin, Griggs and Stillson[15] found exclusive hypertrophy of the right ventricle in 44.1 of 102 necropsies on individuals with pneumokoniosis. The occurrence of right ventricular hypertrophy as a result of pulmonary tuberculosis was long disputed, but was established by Hirsch's[27] measurements of the weights of the individual chambers of the heart. Hypertrophy of the right ventricle is absent or slight in tuberculosis in the young and in cases which run a relatively rapid course, but may be well marked in chronic fibroid phthisis involving a large part of both lungs and with its usual cortège of emphysema and pleural adhesions. Even in these cases of fibroid phthisis it is usually not feasible to demonstrate the right ventricular enlargement during life. Part of the difficulty in the radiographic demonstration of right ventricular enlargement in these patients, even

when it is later found at necropsy to be quite pronounced, is due to the fact that most of the tuberculous have a hypoplastic "drop" heart, the dimensions of which may not exceed the normal after considerable augmentation of the volume of the right ventricle. Boas and Mann[9] found right axis deviation in only 29 per cent of their tuberculous patients, and the percentage was not notably higher in the cases with extensive fibrosis or pleural adhesions.

The cause of the right ventricular hypertrophy in widespread pulmonary fibroses is presumably increased resistance to blood flow through the lungs resulting from destruction of interalveolar septa with their included capillaries. In addition, most of the cases develop well-marked compensatory emphysema.

In these fibroses of the lung, the hypertrophied right ventricle generally maintains an adequate circulation until the terminal stages of the disease, and it is only then, if at all, that swelling of the veins and liver, edema, and other evidences of right ventricular failure appear The cyanosis and dyspnea from which the patients so often suffer for years are almost always predominantly or entirely due to the pulmonary lesions *per se*, and not to circulatory failure I have repeatedly found normal pulmonary circulation time in patients with fibroid phthisis who suffered from severe dyspnea and were markedly cyanotic. Occasionally, protracted insufficiency of the right side of the heart complicates the pulmonary fibroses This generally occurs in older individuals, and it may be that coronary arteriosclerosis is concerned in the pathogenesis of the heart failure

An occasional cause of circulatory embarrassment in patients with pulmonic fibrosis is *displacement of the heart* with resultant kinking of the great vessels This is perhaps most often seen in chronic fibroid tuberculous lesions of the left upper lobe which pull the heart upward and to the left. In such cases, the dyspnea and cyanosis may be very severe

Subcutaneous edema in far-advanced pulmonary tuberculosis is rarely due to heart failure. Much more often, it is a cachectic edema due to hypoproteinemia, a manifestation of amyloid nephrosis, or results from the venous thrombi which are so common in the last stages of phthisis

Widespread *pleural adhesions* have also been considered among the causes of hypertrophy of the right ventricle with ultimate failure. In at least the large majority of the cases, intrapulmonary factors are also concerned. Pleural adhesions may entail circulatory embarrassment with dyspnea and cyanosis through displacement of the heart or compression of the great veins by fibrous bands resulting from a pleuromediastinal inflammation.

PULMONARY ENDARTERITIS

Widespread narrowing of the small pulmonary arteries may increase the work of the right ventricle so much that it is the main or an accessory cause of hypertrophy and ultimate failure of this chamber. Such a succession of events is observed in two main groups of cases.

1. *Arteriosclerosis* and *arteriolosclerosis* of the pulmonary radicals develop as a result of the long-standing hypertension engendered in the lesser circulation by mitral stenosis, pulmonary emphysema, or the fibroses of the lung The resulting clinical and anatomical picture has been described in detail by Moschcowitz,[49] who terms it the syndrome of hypertension of the pulmonary circulation In rare instances, the arteriolosclerosis is so marked that it may add significantly to the work of the right ventricle, and thus play a part in the failure of this chamber There would seem to be little doubt that these secondary arteriolar lesions in the lungs play a significant rôle in the production of dyspnea, cyanosis, and other symptoms in many long-standing cases of mitral stenosis in which the clinical picture approaches that of the "black cardiacs" about to be described The lesions in the pulmonary arteries and arterioles in these cases are similar in structure and pathogenesis to those found in the vessels of the greater circulation in essential hypertension, and are doubtless to be included in the concept of arteriosclerosis In fact, Parker and Weiss[50] have shown that in long-standing mitral stenosis there may even be arteriolar necrosis in the lungs akin to the necrotizing arteriolar changes in the kidney in the malignant phase of essential hypertension.

2 The second group of cases is characterized anatomically by intimal thickening due to proliferation of the endothelium and intimal connective tissue and cellular infiltration of the intima, *i e*, by *endarteritis proliferans* which is presumably of inflammatory origin and therefore not included in the rubric of arteriosclerosis. There may also be inflammatory lesions in the media and adventitia These changes also affect the larger pulmonary arteries

This section is concerned with the second group of cases, *i. e*, that in which pulmonary endarteritis is responsible for the circulatory disturbance It is sometimes known as *Ayerza's disease*, after the Argentinian clinician whose lecture on what was supposed to be this condition was later reported and amplified by his pupils (Arrillaga[2] and Escudero[20]). However, Romberg[58] and others had previously described cases of primary pulmonary "arteriosclerosis" For detailed surveys, the reader is referred to the monographs of Posselt[53] and Ljungdahl,[43] and especially to the recent review of Brenner [10]

Occurrence and Etiology of Pulmonary Endarteritis.—It generally occurs in young or middle-aged adults. The cases are rare in this country and apparently in Europe. I have seen 4 or 5 patients in whom the clinical criteria pointed strongly to pulmonary endarteritis, but apart from the case mentioned below in which the pulmonary lesions were part of a widespread thrombo-arteritis have had no opportunity to check the diagnosis at necropsy. Judging by the reports of Argentinian clinicians, it may be more frequent in that country, although it would seem that they include cases which belong in the first of the above groups. Rogers[57] states that primary pulmonary arterial disease is not rare in Hindus.

Regarding the etiology, little is known. The Argentinian investigators originally considered all the cases syphilitic, but more recently regard syphilis as only one of the causes. Warthin[65] considered the histological evidence of syphilitic causation conclusive in his case, although he was unable to demonstrate spirochetes in the lesions. Many of the published cases are definitely not of syphilitic etiology, and in only a few does this origin seem likely. In Bacon and Apfelbach's[5] cases, the illness apparently dated back to epidemic influenza and pneumonia. They recall that Le Count described frequent necrosis of the minute vessels of the lung in epidemic influenza. Since some of the cases give a history of long-standing cough, the origin of the arterial lesions in long-standing pulmonary infections is suggested. In areas of chronic inflammation in the lungs, endarteritis obliterans is very common, and perhaps some of the cases of pulmonary endarteritis are due to chronic pulmonary infections with predominant arterial involvement. I saw one case in which the pulmonary arteriolar lesions were part of a process widespread throughout the small arteries of the body; they were apparently organized thrombi, and followed a long series of intravenous injections of a vaccine for arthritis. Congenital narrowing of the mouths of the pulmonary veins has been suggested as a cause of the pulmonary arterial lesions, but small pulmonary veins have been found in only a few of the cases and are then probably a result and not a cause of the arterial lesions (see below).

Pathological Anatomy.—The important findings are thickening of the walls of the small pulmonary arteries with narrowing or obliteration of the lumens and hypertrophy of the right ventricle.

The thickening of the walls of the small pulmonary arteries is generally, but not always, visible to the naked eye when the lung is sectioned. Microscopically, it is seen to be due largely to proliferation of connective tissue in the intima and media. Usually, this tissue is poor in nuclei, but sometimes the fixed tissue cells are more numerous and there may be foci of lymphocytic infiltration. Hyalinization and other regressive changes may occur in the thickened intima. Necrosis of the media may occur. Cellular infiltra-

tion of the media and adventitia is common. Some of the vessels may be occluded by fresh or organized thrombi As mentioned above, it is possible that some of the cases are initiated as a thromboangiitis with subsequent organization

The trunk of the pulmonary artery and its first branches are greatly dilated; the former may far exceed the aorta in circumference. These vessels may be relatively smooth or they may present well-marked arteriosclerosis, which is presumably secondary to the hypertension of the lesser circulation Localized aneurysmatic dilatation is rare. Microscopically, the main pulmonary artery may show comparatively little that is abnormal or there may be only atherosclerosis. In other cases, cellular infiltration and other evidences of inflammation are present Warthin considered the findings in his case as typical of syphilitic mesarteritis

The striking feature on examination of the heart is hypertrophy of the right ventricle and usually also of the right auricle As a result, the heart is globular, the apex is formed largely or completely by the right ventricle, and the left ventricle may appear merely as an appendage hardly visible in front In some of the cases, the thickness of the wall of the right ventricle exceeds that of the left ventricle The left side of the heart and the pulmonary veins have been observed to be atrophic and abnormally small, this is presumably a consequence of the small amount of blood they are called upon to handle, the state of affairs being analogous to that of the left ventricle in "pure" mitral stenosis

The state of the lungs is variable Posselt, Eppinger and Wagner,[19] and Bacon and Apfelbach call attention to a pale and bloodless condition of the lungs, which may be small—just the opposite of what is found in failure of the left side of the heart Sometimes, there is emphysema, but in other cases this is slight Small infarcts or bronchopneumonia may be present.

The other organs reveal cyanosis and chronic passive congestion, edema is often massive.

Clinical Picture.—In a number of cases, the clinical picture has been sufficiently distinctive to enable the diagnosis to be established during life In others, the diagnosis has not been suspected until postmortem examination, largely, it would seem, because the possibility of pulmonary endarteritis has not been borne in mind The characteristic picture is one in which deep cyanosis and great enlargement of the right side of the heart are unaccompanied by enlargement of the left heart (especially the left auricle) or marked emphysema

Various types of onset have been observed In some of the cases, there has been a preliminary period of years of cough or asthma, during which the patient is not cyanotic In others, the onset is fairly abrupt with sudden symptoms as dyspnea, palpitation,

thoracic pain, edema and weakness. Cyanosis may precede marked subjective symptoms.

Dyspnea is nearly always present. It is exertional, but there may also be attacks of paroxysmal dyspnea, and a history of previous bronchial asthma is sometimes elicited. In many of the cases, dyspnea is comparatively mild, and it is a characteristic feature that cyanosis is far more pronounced than dyspnea. Orthopnea is generally absent, but may appear toward the end.

Cough is commonly present, but may be absent. Some of the cases have recurrent small *hemoptyses.*

Palpitation and *thoracic pain* may be present. While the pain may simulate that of coronary artery disease, it is often poorly localized within the chest. Peculiar seizures of what has been termed "angina hypercyanotica" have been described, consisting in violent intrathoracic pain accompanied by deepening of the cyanosis.

Somnolence is a striking feature of many of the cases in the last months and is perhaps due to protracted anoxemia. Some of the patients sleep most of the time, and may die in their sleep.

Headache, weakness and *syncope* are other complaints, which may be present over years

Cyanosis is the dominant objective characteristic, for which reason the patients have been called *black cardiacs* by Argentinian clinicians. Indeed, the cyanosis is so deep that the patients often appear blackish-blue for a considerable period. The cyanosis may be as deep as the most intense seen in congenital heart disease. It often becomes more pronounced during episodes of heart failure.

Examination of the *heart* reveals marked enlargement of the right ventricle and almost always also of the right auricle (page 374). The pulmonary conus is greatly enlarged. What is characteristic is that fluoroscopic study shows that the increase in the size of the right heart is not accompanied by enlargement of the left auricle and left ventricle The pulmonic second sound is greatly accentuated, and the diastolic murmur of relative pulmonary regurgitation may be audible. There may be right-sided gallop rhythm. The heart rate is usually moderately accelerated. Arrhythmias other than extrasystoles are rare. The electrocardiogram reveals right axis deviation, usually with inversion of the *T* wave in the third lead. The arterial blood pressure is not characteristically changed.

The *lungs* may reveal surprisingly little. There may be moderate emphysema, but in most of the cases this is not demonstrable. Auscultation may disclose little change in the breath sounds, or there may be scattered râles. Several clinicians have stressed the importance for the diagnosis of unusually light lung fields in the roentgenogram, corresponding to the bloodless state of the lungs

at necropsy, and quite the opposite of what is seen in chronic passive congestion of the lungs. Dilatation of the primary branches of the pulmonary artery may be prominent in the roentgenogram

After the right ventricle has failed, the superficial *veins* and *liver* swell, the venous pressure rises, and dependent *edema* and often *ascites* appear. The edema may become very massive. As a rule, the appearance of edema presages that the end is a matter of months

The *spleen* is palpable in many, though not all, of the cases

It is rather surprising that *clubbing of the fingers* is absent in the large majority of instances.

Ophthalmoscopic examination may show *retinal hemorrhages* and marked *papilledema* In one patient whom I studied, an excellent response of the symptoms of right ventricular failure to digitalization was accompanied by complete clearing up of the retinal hemorrhages and edema.

Polycythemia is present in most of the cases. Red cell counts of over 9,000,000 have been recorded

In many of the cases, the clinical *course* exhibits two quite well-defined stages In the first stage, the objective findings are completely dominated by cyanosis, and evidences of insufficiency of the right ventricle are absent, even though this chamber is greatly enlarged In one case in this stage, with marked cyanosis, I found a normal pulmonary circulation time Such a finding indicates the presence of changes in either the capillaries or the pulmonary parenchyma interfering with gas exchange This initial stage may last for years. In the second stage, the evidences of insufficiency of the right heart are added to those of deficient aeration of the blood in the lungs. Often, the heart failure is rapidly progressive and the patient succumbs within a few months, but in other cases several bouts of heart failure are overcome with appropriate treatment

Carcinomatous Endarteritis and Other Obstructions of the Pulmonary Arteries.—Schmidt,[60] Greenspan,[23] and Brill and Robertson[11] have described cases in which carcinomatous metastases to the lung narrowed the pulmonary vascular bed sufficiently to result in hypertrophy of the right ventricle. In Greenspan's cases, the narrowing of the pulmonary arterioles was due not so much to carcinomatous emboli within these vessels as to obliterating endarteritis resulting from carcinomatous lymphangitis in the perivascular lymphatics In two of the cases described in Greenspan's interesting paper, there were not only dyspnea and cyanosis, which might be due directly to the pulmonary metastases, but also such evidences of right ventricular failure as swelling of the liver and generalized edema. The right ventricular failure may progress so rapidly that Brill and Robertson speak of subacute cor pulmonale

Interestingly enough, similar right ventricular strain and failure

may occur in *schistosomiasis* as a result of blocking of the minute pulmonary vessels.

Yater and Hansmann[73] observed hypertrophy and failure of the right ventricle in two patients with *sickle-cell anemia*. In one, necropsy disclosed thromboses in the small pulmonary arteries, in the other thickening of the walls of the pulmonary arterioles.

Recurrent pulmonary embolism as a cause of chronic right ventricular strain is discussed on page 557.

KYPHOSCOLIOSIS

Most hunchbacks ultimately succumb to heart failure. Thus, Boas[5] quotes the figures of Bachman, who found that 116 of 195 patients with kyphoscoliosis died of cardiac insufficiency.

That heart failure is so common in kyphoscoliosis is hardly surprising. As a result of the thoracic deformity, large volumes of pulmonary parenchyma are compressed and rendered atelectatic. Where the deformity dates back to childhood, some parts of the lung do not develop. Huchard[30] describes a case in which the left lung was smaller than the fist. In other portions, there is compensatory emphysema. Moreover, the great vessels are often kinked. These changes doubtless increase the resistance to pulmonary blood flow and thus strain the right ventricle. The work of the right ventricle may also be increased by paroxysms of violent cough from the bronchitis to which these individuals are so susceptible. Displacement of the heart, abnormal curvature of the aorta in following the spine, and kinking of the vessels leaving the arch of the aorta may also embarrass the left ventricle. In accord with these considerations, Bachman (quoted by Boas) found in 154 cases of kyphoscoliosis, hypertrophy and dilatation of the right ventricle in 87, of the left ventricle in 27, and of both ventricles in 40. From these figures, it is evident that the right ventricle bears the brunt of the circulatory strain in kyphoscoliosis. The hypertension of the lesser circulation is often revealed by accentuation of the pulmonic second sound, although this may be masked or its interpretation rendered difficult by the thoracic deformity. Another consequence of the high tension in the lesser circuit is the pulmonary arteriosclerosis which has repeatedly been found.

Dyspnea and cyanosis, especially on exertion, are often present or many years. It is frequently difficult to determine to what extent these are due to circulatory failure and how far to diminution in the aëration surface and impairment of the ventilation of the lungs. Measurements of the pulmonary circulation time would aid in this differentiation, but apparently have not been carried out. When the right heart finally fails, swelling of the veins and liver

and edema appear. Boas observed paroxysmal auricular fibrillation and states that persistent tachycardia, as well as attacks of palpitation and precordial pain, are common.

TRICUSPID REGURGITATION AND STENOSIS

Apart from excessively rare developmental anomalies and bacterial endocarditis, the latter of which has little effect on circulatory dynamics, organic tricuspid defects are of rheumatic etiology. They are by no means as rare as is often thought. Thus, Cabot[12] found 33 tricuspid stenoses in 220 necropsies on individuals with valvular defects and Dressler and Fischer,[16] in 123 necropsies in cases of endocarditic valvular disease, observed tricuspid stenosis (practically always combined with insufficiency) 30 times and tricuspid regurgitation 8 times. However, such high incidences refer only to postmortem findings. The large majority of the cases are not susceptible of clinical diagnosis. Almost invariably, organic tricuspid defects evolve in patients in whom mitral stenosis had previously reached a considerable severity, and in many of whom there is also aortic valvular disease. Stenosis of all three orifices is by no means a rarity. While tricuspid stenosis on rare occasions becomes so severe that the orifice will not admit the little finger, it is very exceptional that the narrowing is even nearly as tight as that of the mitral valve. Since the mitral valve is thus the point of greatest obstruction to the circulation, it is not surprising that in the vast majority of instances the picture continues to be dominated by the consequences of the pre-existing mitral stenosis Tricuspid stenosis in the absence of significant disease of the other valves is a clinical curiosity; Futcher[22] found only 14 such cases in the literature, and I have not encountered the condition

In the organic tricuspid defects, both stenosis and insufficiency are almost always present by the time of necropsy. The anatomical changes are very similar to those in the corresponding defects of the mitral valve (page 489), except that they are rarely as far advanced as the latter. The pathological physiology and mechanism of compensation are also analogous to those of the left-sided auriculoventricular defect Even well-marked tricuspid defects may be well compensated for years, as is sometimes shown by the finding of an obviously old stenosis at the necropsy of an individual who had had symptoms of heart failure for only a short time.

Functional tricuspid insufficiency (page 402) is a manifestation of dilatation of the right ventricle The latter is almost always secondary to hypertension of the lesser circulation engendered by failure of the left side of the heart in mitral, aortic, hypertensive or arteriosclerotic disease, or by emphysema. Such functional incompetence is by far the most common cause of dynamically significant

tricuspid regurgitation. Even when lesions of the tricuspid valve are found at the necropsy of a patient with rheumatic heart disease who presented clinical evidence of tricuspid leakage, the functional element is usually the more important in the production of the latter.

Clinical Manifestations of Tricuspid Defects.—From the foregoing, it will be evident that tricuspid defects are almost always merely complications of pre-existent cardiac lesions. The former can rarely be said to have a clinical picture of their own, and the following will be confined to a description of the modifications in the symptomatology of mitral stenosis which result from the development of tricuspid obstruction *Only exceptionally are these sufficiently characteristic to enable the recognition of the complication* The manifestations of tricuspid regurgitation have already been discussed (page 402)

Dyspnea and sometimes orthopnea are present in patients with heart failure resulting from mitral and tricuspid stenosis, and may be very severe However, Futcher, Herrick[26] and others have observed that in some of the cases the dyspnea is remarkably slight and the patient unusually comfortable despite a huge liver, ascites and massive edema I have been struck in several such cases by the absence of orthopnea. It is to be presumed that the amelioration of the dyspnea and orthopnea is due to the tricuspid obstruction militating against pulmonary engorgement. However, the phenomenon, even when present, is not characteristic of tricuspid stenosis, for we have seen that the same relief of dyspnea often follows failure of the right ventricle in the absence of tricuspid stenosis (page 505)

Cyanosis is present in the large majority of patients with tricuspid stenosis and heart failure. While the cyanosis is often very deep, this is not characteristic, for equally deep cyanosis may occur in uncomplicated mitral stenosis. Cyanosis may be totally lacking in compensated tricuspid stenosis. Paroxysmal cyanosis, akin to that seen in congenital heart disease, has been observed in tricuspid stenosis. The cyanosis is not uncommonly mixed with faint icterus (cyanotic icterus), but this also occurs in decompensated mitral disease.

Examination of the heart reveals broadening to the right resulting from enlargement of the right ventricle and especially the right auricle. The enlargement of the right ventricle also leads to a precordial heave and epigastric pulsation. But these phenomena may also result from mitral stenosis In a patient who was under observation at Montefiore Hospital for sixteen years with a heart almost reaching the right axilla, because of which tricuspid disease was suspected, mitral stenosis was found at necropsy. It might be thought that the auscultatory findings would be helpful in the detection of tricuspid lesions, but this is rarely the case. A systolic

murmur of maximum intensity in the xiphoid region and transmitted better to the right is heard in only a fraction of cases of tricuspid leakage, and may be due to functional insufficiency. As in all parts of the precordium, systolic murmurs in the xiphoid region may be heard in healthy people The characteristic diastolic or presystolic murmur of tricuspid stenosis, heard best in the

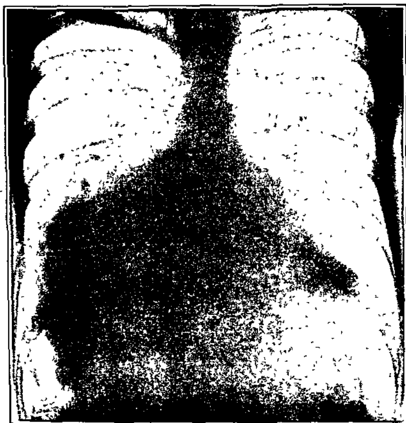


Fig 21 —Enormous enlargement of the right side of the heart in a patient with tricuspid and mitral stenosis

xiphoid region and to the right of the sternum, is a rarity, and is not heard in many cases which prove at necropsy to have moderate or even considerable tricuspid narrowing. Absence of the accentuation of the pulmonic second sound which is usually present in decompensated mitral stenosis has been regarded as evidence of complicating tricuspid stenosis, but may result from right heart failure without such complication. The electrocardiogram gener-

tricuspid regurgitation. Even when lesions of the tricuspid valve are found at the necropsy of a patient with rheumatic heart disease who presented clinical evidence of tricuspid leakage, the functional element is usually the more important in the production of the latter.

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pronounced. However, dyspnea on exertion or paroxysmal dyspnea is present in some of the cases for years before the appearance of cyanosis. Many deeply cyanotic patients have little dyspnea and no orthopnea. In fact, French clinicians have observed that the dyspnea of pulmonic stenosis may be less in the recumbent position (orthostatic dyspnea). The disability of most patients with pulmonic stenosis is due more to weakness than to dyspnea When the right heart failure of pulmonic stenosis becomes manifest in the form of swelling of the systemic veins and liver and edema, the end is usually not far off. Cyanosis retinæ and rarely convulsive seizures are other manifestations of pulmonic stenosis.

The appearance of cyanosis in pulmonic stenosis is favored by the polycythemia, as a result of which cyanosis becomes manifest at lower oxygen unsaturation of the blood (page 183). The cyanosis is apparently precipitated by two mechanisms: (1) As a result of right heart failure, the venules are distended and peripheral blood flow slowed, (2) in a high proportion of the cases the foramen ovale is widely patent. This is apparently a secondary phenomenon resulting from the high pressure in the right side of the heart due to the pulmonic stenosis. The high pressure in the right heart may, at least at times, result in flow of venous blood from the right auricle through the patent foramen ovale into the left heart and thus produce cyanosis. This second mechanism is probably responsible for cyanosis in patients with pulmonic stenosis who have few other evidences of right heart failure.

Pulmonic Regurgitation.—Organic pulmonic regurgitation is a great rarity. Functional pulmonic regurgitation is discussed on page 405.

ACUTE RIGHT VENTRICULAR FAILURE IN PULMONARY EMBOLISM

Pulmonary embolism may occasion right ventricular failure of a severity and acuity hardly duplicated under other circumstances The clinical picture of bland pulmonary embolism is largely determined by the size of the vessel occluded. In a general way, three groups of cases may be distinguished:

1. Occlusion of the trunk or first branches of the pulmonary artery, which, when not immediately fatal, results in acute insufficiency of the right side of the heart, but only exceptionally produces infarction. The picture may closely resemble that of myocardial infarction or spontaneous pneumothorax.

2. Occlusion of one or more middle-sized branches, which is often asymptomatic and merely a postmortem finding, or may result in pulmonary infarction and perhaps shock. These cases have already been considered (page) 235.

3. Occlusion of minute branches or capillaries, which is most often clinically latent. However, in rare instances the emboli are so numerous as to produce acute circulatory failure akin to that of embolization of the primary branches

Embolization of the Trunk and Main Branches of the Pulmonary Artery.—In order to plug such large vessels as the pulmonary trunk or its first branches, an embolus must be of large size. For this reason, the emboli in question rarely come from the right side of the heart. Almost always, they emanate from the veins of the lower extremities and perhaps also the pelvis, where clots often form which are so long that, when coiled like a snake or folded on themselves, they can completely occlude the pulmonary trunk or its first branches. Even when pulmonary emboli of the massive type here under discussion occur in mitral stenosis or other forms of heart disease, they usually emanate, not from the right heart, but from the veins of the lower extremities. Indeed, Aschoff[3] states that by carefully unfolding pulmonary emboli he "has always been able to prove that one is dealing here with blood clots 35 to 45 cm. in length," and that "the only vessel which comes into play as a possible source is the femoral vein." These points are brought out to emphasize how important it is to examine carefully the veins of the lower extremities in bed-ridden patients. Unfortunately, massive embolization not rarely occurs from veins which present little external evidence of inflammation or thrombosis.

The causes of venous thrombosis in the lower extremities will not be discussed here in detail. (See the classical article of Welch.[70]) Suffice it to say that the most common occurrence of embolization of such clots is about the second or third week after abdominal operations, especially those on the female pelvic organs and prostate and the victims of carcinoma, in the same period of the puerperium, in prolonged venous stasis due to heart failure; and in infectious phlebitis of the lower extremities, especially when the latter does not occur in varicose veins How important a rôle intravenous injections play in the increase in thrombosis and embolism first observed in Germany following the first World War has not been established; in any event, emboli from the upper extremity are rarely of the type here under discussion, being generally only large enough to occlude a medium-sized or small artery.

Clinical Picture.—Complete plugging of the trunk of the pulmonary artery is, of course, quickly fatal. It accounts for the most tragic of accidents following operation or delivery. Usually about the second week after the event, often when the patient sits up for the first time, she suddenly gasps and is dead before anyone can reach her. Or she may cry out, become pale, then perhaps cyanotic and almost black, and succumb within seconds or minutes. Similar quick death may occur after occlusion of only one of the main

branches, or after incomplete plugging, various unproved hypotheses, including reflexly induced spasm of the pulmonary arteries, have been advanced in the effort to explain such an occurrence.

In other cases of massive but incomplete embolic occlusion of the trunk or first branches of the pulmonary artery, death is not so nearly instantaneous and exceptionally recovery ensues Hampton and Wharton[25] found that of their patients with pulmonary embolism following gynecological operations, 50 per cent succumbed within thirty minutes, 25 per cent between fifteen and twenty-four hours after the occlusion, and 10 per cent recovered *The clinical picture in these cases of massive pulmonary embolism which do not succumb immediately is a remarkable combination of shock and systemic venous engorgement due to the acute failure of the right ventricle.* In a brilliant contribution which initiated the present intensive study of the subject, McGinn and White[47] term it *acute cor pulmonale* The onset is sudden, usually dramatic The first symptom is almost always suffocation of agonizing severity Sometimes, the first complaint is of pain in the sternal region, either side of the chest, or in the shoulder. However, the dyspnea is so overpowering that it is not always differentiated from pain in the ordinary sense, and the patient is in no condition for precise questioning Occasionally the sufferer, especially if hyposensitive, simply complains of weakness and faintness Collapse may be the only manifestation with little indication of respiratory embarrassment. The patient cries for aid, or may be too weak to do so. Consciousness is sometimes retained practically to the end, or the sufferer may lapse into coma Twitchings or convulsions occasionally occur, and there may be involuntary passage of urine and feces Not rarely, there is temporary improvement followed by quick death as the plugging becomes more complete or a fresh embolus completes the occlusion.

The objective findings in massive pulmonary embolism are produced by the acute right ventricular failure and belong in three categories: manifestations of shock due to decreased cardiac output, results of the intense engorgement of the systemic veins, and evidences of the dilatation of the right heart and pulmonary artery. When shock dominates, the patient is ashy pale, covered with profuse perspiration which may soak through the bedclothes, the extremities are cold, the pulse hardly if at all palpable, and the arterial tension low. The insufficiency of the right side of the heart results in intense swelling of the veins of the neck and rapid enlargement of the liver. Remarkable in some cases is that the engorgement of the cervical veins is accompanied by constriction of the veins in the extremities (page 656) The initial pallor may be replaced more or less rapidly by cyanosis which may become almost black. The heart rate is rapid until the terminal (probably anoxemic) slowing, embryocardia is common, and the pulmonic second

sound may be accentuated. Lord[48] and others have been able to demonstrate by percussion the dilatation of the right heart that is found at postmortem A rough systolic murmur accompanied by a thrill in the second left interspace has been heard. Among the other physical signs described by McGinn and White are palpability of the dilated pulmonary artery in the second left interspace, what sounds like a pericardial friction rub in this location, and also gallop rhythm best heard in the second and third interspaces to the left of the sternum Examination of the lungs soon after the occlusion generally reveals little abnormal. It has been said that when one branch is occluded, this side may lag in breathing Râles generally develop after a time in one or both sides, and widespread pulmonary edema may appear at the end. In embolism of the pulmonary artery without infarction, Westermark[71] has observed ischemia of the branches of the pulmonary artery distal to the obstruction resulting in a clarified area with diminished vascular markings Fever and leukocytosis are common.

It is evident that the picture closely resembles that of myocardial infarction affecting the interventricular septum, which also causes the combination of shock with systemic venous engorgement. Hamburger and Saphir,[24] Averbuck,[4] and McGinn and White have pointed out how difficult may be the differential diagnosis between pulmonary embolism and coronary thrombosis I have known this dilemma to occur on a number of occasions, as well as confusion with spontaneous pneumothorax. Usually, the circumstances under which the vascular accident occurs indicate the diagnosis Often, the characteristic electrocardiographic findings of myocardial infarction show that this is present. However, it must be borne in mind that pulmonary embolism may also cause electrocardiographic changes, which may indeed be sufficiently characteristic to lead to the suspicion of or confirm the diagnosis (McGinn and White, Barnes[6]) These electrocardiographic changes in pulmonary embolism were originally described by McGinn and White as follows: "The changes that appear significant are the presence of a *Q* wave and late inversion of the *T* wave in Lead III, the rather low origin of the *T* wave with a gradual staircase ascent of the *S–T* interval in Lead II, a prominent *S* wave and a slightly low origin of the *T* wave in Lead I, and an inverted *T* wave with upright *P* and *QRS* waves in Lead IV." In some of their cases the electrical axis shifted to the right. Particularly important for the differentiation from the electrocardiographic changes of posterior myocardial infarction, with which the electrocardiogram of pulmonary embolism is most apt to be confused, is the development of a large *S* wave in Lead I and of inversion of the *T* wave in the precordial lead. The typical electrocardiogram described by McGinn and White does not occur in by any means all instances of pulmonary

embolism (*cf.* Sokolow[62] *et al.*). But Barnes points out that it is especially apt to occur in massive pulmonary embolism which produces the clinical picture of acute right heart failure described above, and this has also been my experience. In all probability the electrocardiographic changes characteristic of pulmonary embolism are manifestations of ischemia of the right ventricle, induced on the one hand by the enormous increase in the work of this chamber and on the other by the impairment of the blood flow to the right ventricular myocardium due to the pronounced increase in the pressure within the right side of the heart. Also understandable on the basis of ischemic pathogenesis are the transient bundle branch block (Durant *et al*[17]) and other transient electrocardiographic changes that have been observed in pulmonary embolism Good support for the conception of ischemic damage to the myocardium in massive pulmonary embolism is afforded by the observation of fresh myocardial necrosis by Horn, Dack and Friedberg.[29]

Repeated Pulmonary Embolism.—Successive emboli, some large, may lodge in the lungs over a period of months. These emboli become organized and the obstruction they cause may be augmented by superadded thrombosis. Belt[7] has described cases of this type, and believes that such recurrent embolism may cause chronic cor pulmonale with the picture of "Ayerza's disease" (page 541).

Emboli in the Small Pulmonary Arteries.—As already mentioned, embolization of the small pulmonary arteries generally produces no clinical manifestations. Such emboli probably occur in a high proportion of instances of venous thrombosis It seems plausible that minute emboli often result in tiny infarcts in patients with passive congestion of the lungs, and thus are one of the causes of the blood-streaked sputum so common in such cases.

Bland emboli in the small pulmonary arteries and capillaries become of clinical significance only when they are exceedingly numerous. This occurs under two unusual circumstances, namely, air and fat embolism. In the extremely rare cases in which a high proportion of the pulmonary vessels are embolized by gas or fat, there may be an extremely severe and sometimes rapidly fatal clinical course resembling that of massive embolism of the pulmonary trunk—violent dyspnea, cyanosis, feeble or impalpable pulse, other features of shock, and engorgement of the systemic veins. It is thought that these symptoms are due not only to the interference with the gas exchange in the lungs, but even more to the emboli so increasing the resistance to blood flow through the lungs that the right ventricle fails There may be convulsions, coma, hemianopsia, and other cerebral symptoms, in which cerebral emboli may be concerned, though these may also apparently result entirely from anoxemia due to the pulmonary plugging In the case of air embolism, some believe that the circulatory failure is not due entirely

to the plugging of the pulmonary vessels, but that air trapped in the right ventricle may cause dilatation and failure of this chamber. A churning sound has been heard over the heart, and it is said that the percussion note in this region may be tympanitic. For details concerning gas and fat embolism, the reader is referred to Welch.[70]

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CHAPTER XXIX

HEART FAILURE INITIATED BY GENERALIZED CARDIAC STRAIN: I. ACCELERATION OF THE CIRCULATION

In the preceding chapters we have seen that the large majority of instances of heart failure are initiated by strain of either the left or, far more rarely, of the right side of the heart. In left-sided failure there is usually subsequent strain and insufficiency of the right ventricle. There are, however, also varieties of hyposystolic heart failure in which the initial strain involves simultaneously all the chambers of the heart. This occurs under two diametrically opposed circumstances:

1. Acceleration of the circulation with increase in the venous return to the heart.
2. Diffuse myocardial disease.

ACCELERATION OF THE CIRCULATION

Acceleration of the circulation is manifested by an increase in the venous return to the heart. Since the heart must pump this increased minute volume of blood, there is corresponding augmentation in the work of each of the cardiac chambers. The conditions characterized by protracted acceleration of the circulation with consequent increased work and strain of all the cardiac chambers are: hyperthyroidism, anemia, fever (see Chapter XXXII), arteriovenous fistula, and hypoglycemia. It will be seen in the following that before the overwork of the heart leads to failure, there is usually, if not always, diminution in the functional capacity of the myocardium. Hard labor and athletics are forms of physiological acceleration of the circulation which increase the work of the heart and thus produce hypertrophy, but do not *per se* lead to failure.

Hyperthyroidism.—In hyperthyroidism the work of all the chambers of the heart is increased. The heart is almost always equal to the task in the young, but in the elderly cardiac failure may develop. In fact, since the determination of the basal metabolism has become an everyday procedure, it has become evident that the initial clinical manifestations of hyperthyroidism may be those of heart failure or of auricular fibrillation, the thyrogenic origin of which may not be evident until the oxygen consumption is measured.

Adaptation of the Circulation to the Increased Metabolism in Hyperthyroidism.—The outstanding feature of the circulation in hyperthyroidism is an increase in the cardiac output, which is largely,

although probably not entirely, an adaptation to the enhanced metabolic rate.

Oxygen consumption is greatly increased in hyperthyroidism; it often exceeds the normal by 50 per cent and rarely 100 per cent. As shown by Plesch,[85] and by more accurate methods by Liljestrand and Stenstroem and Fullerton and Harrop, the greater amount of oxygen consumed in the tissues is delivered by an increase in the volume of circulation. The cardiac output in hyperthyroidism may be more than double the normal. Indeed, the observations of Liljestrand and Stenstroem,[68] Fullerton and Harrop,[31] and Gladstone[35] reveal that the cardiac output is augmented proportionally more than is the oxygen consumption, for they found a subnormal arteriovenous oxygen difference. This is also shown by the finding of Boothby and Rynearson[14] that the cardiac output in hyperthyroidism is greater than that for equal oxygen consumption during work by a healthy person. Grollman[42] points out that the relatively greater increase in cardiac output than in oxygen consumption indicates that the former is not entirely a direct adaptation to the latter It seems plausible that part of the augmentation in cardiac output is due to the increase in blood flow through the skin, which helps to dissipate the preternaturally great amount of heat produced incidental to the increase in oxidative metabolism. The flushed skin and warm hands often testify eloquently to the copious blood flow through the skin The difference between rectal and skin temperature may be subnormal, indicating a relatively greater increase in cutaneous blood flow. Boas[11] has called attention to another factor which tends to increase the cardiac output, namely, the great vasodilatation in the thyroid gland which is so evident at operation He points out that the vascular dilatation in the thyroid gland may be so pronounced as to approach the effect on circulatory dynamics of an arteriovenous aneurysm and produce an increase in cardiac output as does the latter (page 580)

In hyperthyroidism the increment in cardiac output during exercise is abnormally great and there is a delay in the return to the resting volume of circulation after the cessation of effort (Bansi and Groscurth[3]). These abnormalities are probably largely a result of the fact that the "cost of work" is greater in hyperthyroid patients; they increase their oxygen consumption for a given task more than does a healthy person (Plummer and Boothby,[84] Smith,[98] Briard[16] *et al*) Plummer and Boothby attributed this not only to useless movements in performing a task, but also to greater oxygen consumption for the same movements. On the other hand, Briard and her associates believe that there is no basic change in muscle metabolism in Graves' disease but that the increased cost of work is due to enhanced muscle tone and purposeless movements.

The enhancement in cardiac output is accomplished more through

increase in rate than in stroke volume. However, the measurements of cardiac output cited above show that the stroke volume may also be considerably increased (to 83 cc. in one of Liljestrand and Stenstroem's[68] subjects).

Formerly, it was thought that in many patients with large goiters, compression of the trachea is an important factor in increasing the work of the right ventricle and thus producing cardiac failure. The conception was that the tracheal compression increased intra-alveolar tension and consequently the resistance to blood flow through the lungs. There seems to be little evidence that this mechanism is actually significant. Of course, large goiters, especially substernal, may produce dyspnea, cough, and even sudden death by pressure on the trachea. And pressure on the veins may produce venous engorgement in the territory of the superior vena cava. But these manifestations—which are rare in this country because of surgical intervention—do not indicate heart failure.

Morphology of the Heart in Hyperthyroidism.—In view of the increase in the work of the heart in hyperthyroidism, one would anticipate cardiac hypertrophy. That this occurs has been demonstrated experimentally. Simonds and Brandes[97] fed dogs 10 grams of thyroid extract daily for as long as one hundred days. Except where emaciation was extreme there resulted a marked increase in the ratio of the heart weight to the body weight with hypertrophy of all the chambers of the heart, the left ventricle being most affected. Similarly, Smith and MacKay[100] found evidence that the heart weight increases with the metabolic rate when thryoid is administered to rats. Further evidence that increase in metabolic rate entails cardiac hypertrophy is contained in the observations of Boas and Landauer[12] on Frizzle fowl (page 566). They found that this variety of chicken, which has a high metabolism apparently because of scanty plumage, exhibits a significantly greater ratio of ventricular to body weight than does the normal fowl. That elevation in basal metabolism produces cardiac hypertrophy is indicated by the observation of Minot and Means[78] that in chronic leukemia, in which the metabolic rate is often elevated, the heart weight averages about 75 grams above the normal; of course, the possibility that anemia may play a part in producing the hypertrophy must be taken into consideration.

Postmortem Findings.—Recent studies of the heart in hyperthyroidism, in which essential hypertension and other causes of cardiac enlargement are carefully eliminated, reveal hypertrophy in a considerable proportion of the cases. That hypertrophy is not more often revealed by the absolute weight or measurements of the heart is probably due to the fact that many who succumb to Graves' disease are severely emaciated, and the heart shares in the emaciation. Weller[104] and his associates observed that the heart in exophthalmic goiter averages 60 grams more than in a control series, a difference that they consider within the limits of error; however,

they apparently did not take the body weight into consideration. Parkinson and Cookson[82] found cardiac hypertrophy in 22 of 43 instances of Graves' disease. In 89 necropsies on individuals succumbing to hyperthyroidism, Kepler and Barnes[65] found that in 49 per cent the weight of the heart exceeded Smith's maximal standard value for the usual weight of the patient prior to the onset of the illness. If the actual weight at the time of death was used for comparison, Kepler and Barnes found that the weight of the heart practically always surpassed Smith's maximal normal. But in some of their severely emaciated patients (*e g.*, one who had lost 48 per cent of her body weight) the weight of the heart was under the minimal normal Such small hearts may occur despite long duration of the hyperthyroidism, as in a case of Barker, Bohning and Wilson[4] of four years' duration and heart failure in the last two months. Most often the hypertrophy is moderate, but exceptionally a heart weight exceeding 500 grams is encountered for which no cause other than hyperthyroidism is evident. Usually, the hypertrophy affects the whole heart, although either ventricle, more often the left, may be predominantly enlarged In a general way, and with many exceptions, hypertrophy tends to be more pronounced the longer the duration of severe hyperthyroidism and the older the patient Of course, in interpreting cardiac hypertrophy in older patients one must bear in mind the frequency of essential hypertension as a complication of hyperthyroidism Apparently, very severe hyperthyroidism favors hypertrophy, for the latter was present in 7 of Kepler and Barnes' 9 patients with basal metabolic rate exceeding +100 per cent. Hypertrophy is more likely to be found in those who suffered from heart failure than in those who did not. Moderate dilatation is common, especially when auricular fibrillation and heart failure existed.

While the observations cited leave no doubt that hyperthyroidism produces cardiac hypertrophy, the latter is not as massive as might be anticipated from the great increase in the work of the heart. With doubling in the work of the heart as a result of twofold increase in minute volume, the hypertrophy is far less than is seen in, for example, essential hypertension with less than doubling in the work of the heart as a result of augmented resistance in the aorta. The lesser hypertrophy in hyperthyroidism is probably due to the fact that, as a result of tachycardia, the increased work is accomplished more by augmentation in the rate of the heart than in the work per stroke (page 562).

Regarding the *histological changes* in the myocardium, it seems safe to say that specific lesions have not been established. In many of the cases, including some of long duration and with auricular fibrillation and heart failure, there is present no more than the cloudy swelling and fatty change to be found in most protracted

illnesses. Fahr,[28] Goodpasture,[39] and others have described extensive lymphocytic and histiocytic infiltration, areas of necrosis of the heart muscle, and widespread interstitial fibrosis. Such lesions, however, are present in only exceptional cases. The observations of Rake and McEachern[89] and Weller[106] and his associates showed little more morphological evidence of myocardial damage in Graves' disease than in control series The results of experimental investigations have been contradictory. Following the administration of thyroid substance or thyroxin to rabbits, Goodpasture and Menne[75a] and his co-workers, and others observed fatty changes, necrosis, cellular infiltration, and fibrosis of the myocardium. On the other hand, Rake and McEachern were unable to produce lesions in rabbits which differed from those present in controls, and in guinea-pigs observed notable changes almost exclusively in those animals which developed spontaneous pneumonia. These observations and those of Goodpasture suggest that in the very exceptional cases in which severe myocardial lesions occur in Graves' disease they may result from metabolic changes in the muscle fibers due to overwork, which predispose to damage by toxic agents. A significant factor in this regard, as pointed out by Rake and McEachern, may be the great depletion of the glycogen content of the heart muscle which Andrus[2] and others have demonstrated in experimental hyperthyroidism.

Circulatory Manifestations in Hyperthyroidism Without Heart Failure. —The circulatory picture of hyperthyroidism is dominated by overaction of the heart and rapid peripheral blood flow.

Subjective Symptoms.—Palpitation is the most common complaint referable to the heart. It varies from mere consciousness of the activity of the heart to a most distressing pounding. Palpitation usually accompanies marked tachycardia but may also occur with a heart rate of less than 90 per minute. It may be continuous or evoked only by excitement, exertion, or paroxysms of auricular fibrillation. Roesler[95] has found fluoroscopically that the systolic contraction of the ventricles is effected with great rapidity in Graves' disease, a factor which is perhaps concerned in the genesis of the palpitation. Throbbing in the vessels of the neck or in the head may be an annoying complaint.

Precordial pain is not uncommon in hyperthyroidism at all ages, having been present in about 16 per cent of Lerman and Means'[62] patients. Usually it is mild and is described as an ache or soreness in the precordial or retrosternal region. Occasionally, however, severe and typical angina pectoris appears in patients with hyperthyroidism (Lev and Hamburger[63]). Inasmuch as the patients are almost always elderly, it is possible that they have coronary arteriosclerosis; this has seemed probable in the cases that I have seen But since Lev and Hamburger have shown that the angina may be

removed by subtotal thyroidectomy, it would appear that the hyperthyroidism, presumably through increasing the work and shortening the rest period of the heart, is the factor that precipitates the pain.

Exertional *dyspnea* is a common symptom in hyperthyroidism, even in the absence of heart failure. Means[75] attributes the shortness of breath to the diminution in the respiratory factor of safety which results from the coincidence of increase in ventilation due to greater oxygen consumption and decrease in vital capacity. Interestingly enough, Burnett and Durbin[17] found that in the rarefied atmosphere of Denver dyspnea is the most common symptom of hyperthyroidism.

Tachycardia.—Objectively, the most common finding is tachycardia. Sturgis and Tompkins[102] observed a general parallelism between the metabolic and pulse rates. Much closer than the correlation between the metabolic and pulse rates is that between the former and the sum of the pulse rate and pressure. (See Jenkins[53] for statistical analysis *) This is as would be anticipated, for the fundamental parallelism is between the minute volume of the heart and the metabolic rate, and the former is a function not only of the rate of the heart but also of the stroke volume, the latter of which is very roughly proportional to the pulse pressure. In active Graves' disease the basal pulse rate is usually between 80 and 120 per minute but may be considerably faster. During an acute exacerbation of hyperthyroidism (thyroid crisis), usually occurring postoperatively or as the result of an infection, the pulse rate may rise to 200 per minute, being perhaps the fastest of sinus tachycardias. On the other hand, there are also unusual instances of active hyperthyroidism (basal metabolic rate, +40 per cent or more) in which the basal heart rate is less than 80 per minute; they have been referred to as "vagotonic" Graves' disease, but the explanation of the relatively slow pulse rate is obscure. The pulse rate in hyperthyroidism is labile, mounting under slight excitement or exertion, and the difference between the rate during the activities of the day and the basal rate is more than normal. Boas[10] has found that, contrary to psychoneurotic tachycardia, the heart rate in hyperthyroidism is slowed but little during sleep. While his normal controls had an average minimum sleeping pulse rate of

* This has been applied by Read[90] in his formula for the prediction of the basal metabolism

$$\text{Basal rate} = 0.75\,(\text{pulse rate} + 0.74\ \text{pulse pressure}) - 72$$

Read found that with this formula the metabolic rate can be predicted within 10 per cent in over one-half the cases. According to Hunt, Read's formula seldom gives too high an estimate of the metabolic rate but often yields somewhat low results. More recently, Read and Barnett[91] have modified the prediction formula to increase its accuracy. In applying the formula, it is important that one use the pulse rate and pressure when the subject is in the basal state, and not random figures during the day

58 per minute, in Graves' disease this averaged 89 per minute. The rhythm of the heart is generally regular, but there may be paroxysmal or continuous auricular fibrillation or rarely flutter.

It has been generally accepted that the tachycardia of hyperthyroidism is primarily regulatory in nature, and part of the mechanism by which cardiac output is elevated to the level necessitated by the enhanced metabolic rate * This is in good accord with, although not proved by, the fact that the pulse slows when the metabolic rate is decreased by iodine or thyroidectomy. The conception that the tachycardia is a result of the enhanced metabolism was supported by the finding of Minot and Means[78] that approximately the same pulse rates accompany equal elevations of oxygen consumption in hyperthyroidism and chronic leukemia. On the other hand, Friedgood[30] found that there is sometimes a much slower pulse rate in chronic lymphatic leukemia than is usual for the same metabolic rate in hyperthyroidism. The latter observation indicates that, in addition to the elevation of the metabolic rate, other factors, discussed in the next paragraph, participate in accelerating the hyperthyroid heart.

How the increased metabolic rate accelerates the heart is not entirely clear. It may be accepted that the greater metabolic activity in the tissues augments the venous return and consequently the cardia output. However, in the heart-lung preparation increased venous return augments cardiac output not through accelerating the rate but through enhancing stroke volume (page 301) This is contrary to the usual state of affairs in hyperthyroidism, in which the increased venous return is mastered more through tachycardia than through increasing the output per beat. It has therefore been thought that nervous influences are of great importance in the tachycardia, a conception which is in good accord with other evidences of sympathetic hypertonus in Graves' disease. However, recent investigations have brought out another and perhaps predominant factor in the pathogenesis of the tachycardia, namely, the effect of thyroxin on the metabolism of the heart itself. Lewis and McEachern,[67] Yater,[112] and Priestley, Markowitz and Mann[91] have found that if a rabbit is rendered hyperthyroid by thyroid feeding and the heart then removed, the isolated organ continues to beat at a rate much faster, sometimes by more than 50 per cent, than the heart of a normal control. Yater found that the accelerated rate persists after crushing the bundle of His, and Markowitz and Yater[73] showed that thyroxin accelerates the rate of pulsation

* Instructive observations on the correlation of the metabolic and pulse rates have been made by Boas and Landauer[12] They studied the Frizzle fowl, a variety of chicken with a high metabolic rate apparently due to greater heat loss resulting from scanty plumage Boas and Landauer found that the Frizzle roosters had an average minimum pulse rate of 287 per minute as contrasted with 172 per minute in normal roosters

of fragments of heart muscle removed from chick embryos before the development of nerve elements in the heart These experiments show that thyroxin accelerates the heart beat by direct action on the muscle fibers. It is probably largely this factor which accounts for the fact that the heart is accelerated so much more when its work is increased in Graves' disease than by an equal increment in cardiac work due, for example, to hypertension.

Signs of Overaction of the Heart.—In addition to the tachycardia, other manifestations of overactivity of the heart are often evident. There may be prominent and diffuse precordial pulsation; but its force as elicited by palpation does not parallel its prominence. The carotids, and indeed the head, may beat furiously. Because of the widespread pulsation there may be the impression of a larger heart than is subsequently revealed by fluoroscopy. The apex impulse may be preceded by a short vibration and the closure of the pulmonic valve palpable. The heart sounds are generally loud and abrupt; in one of Graves'[41] original cases they could be heard 4 feet away. Sometimes the auscultatory findings at the apex simulate a short presystolic murmur and the abrupt first heard sound as heard in mitral stenosis; the similarity may be heightened by accentuation of the pulmonic second sound and the radiographic findings to be described. A systolic murmur is very common Often it is loudest over the pulmonic area; it may then originate from dilatation of the pulmonic artery (see below). The murmur over the pulmonic artery may have a scratching quality and simulate a pericardial rub, this is especially apt to be the case when the overaction of the heart is pronounced and also occurs in various sthenic fevers. A cardiorespiratory murmur may be audible near the left border of the heart. Diastolic murmurs have been described in Graves' disease, but I have not heard them in uncomplicated cases

The Size and Contour of the Heart.—Cardiac enlargement may result from hyperthyroidism. Only exceptionally are the cardiac dimensions sufficiently enhanced to be unequivocally demonstrable by physical examination, especially in the light of the abovementioned fact that the overaction of the heart may simulate outward displacement of the apex. Radiographic methods are alone reliable for the study of the size and contour of the goiter heart Even with radiography, widely divergent incidences of cardiac enlargement have been reported in hyperthyroidism, probably largely as a result of differences in the type of material. On the one hand, Hurxthal[52] considers significant cardiac enlargement rare in hyperthyroidism unless due to a complication; a similar view was expressed by Cabot.[19] But most recent investigators have found a considerable incidence of cardiac enlargement in uncomplicated hyperthyroidism Thus, Parkinson and Cookson[82] observed

enlargement of the heart in 45 per cent of their cases, Margolies, Rose and Wood[72] in 26 per cent, and Lerman and Means[62] in 29 per cent of male and 42 per cent of female patients. Under thirty years of age, unequivocal cardiac enlargement is rare in uncomplicated hyperthyroidism of even maximal severity. Of course, this does not mean that hypertrophy is not present, for the latter may be considerable without increasing the dimensions of the heart to above the upper limits of normal In older patients with hyperthyroidism, demonstrable enlargement of the heart becomes more frequent with advancing years and is very common after the age of fifty even in the absence of diastolic hypertension or other complication The heart is enlarged in almost all individuals with continuous auricular fibrillation or cardiac failure. The enlargement is rarely more than moderate The connection with hyperthyroidism is often demonstrated by decrease in size following thyroidectomy. In some cases, Parkinson and Cookson observed increase in the dimensions of the heart following operation, which they attribute to upward displacement of the diaphragm as a result of gain in weight Hurxthal and Margolies, Rose and Wood suggest that such enlargement may be a manifestation of postoperative hypothyroidism

The enlargement may be toward both the left and the right so that the heart tends toward a globular shape In other cases, as pointed out by Kerr and Hensel,[56] the enlargement is toward the left and may be accompanied by prominence of the pulmonary arc The latter straightens out the left border or produces a bulging convexity. In some cases the prominence of the pulmonary arc is the only abnormality of the cardiac contour, which may thus simulate the appearance of mitral stenosis on dorso-ventral illumination. However, examination in the first oblique diameter shows that in hyperthyroidism there is no considerable enlargement of the left auricle. The prominence of the pulmonary arc is due to dilatation of the pulmonary artery, presumably in consequence of the large volume of blood flow. Parkinson and Cookson were able to demonstrate this dilatation of the pulmonary artery at necropsy. The pulsation of the borders may be prominent; as pointed out by Roesler,[95] the systolic indrawing of the borders occurs with abnormal rapidity. The pulsation of the pulmonary artery is apt to be especially pronounced.

Electrocardiographic Findings.—Apart from the accelerated rate, the overactivity of the heart in Graves' disease finds little repercussion in the electrocardiogram. Hoffmann[48] and Krumbhaar[55] long ago described an increase in the amplitude and duration of the *T* wave, just as low *T* waves are the rule in myxedema. McGuire and Foulger[70] were able to produce increase in the voltage of the *T* wave by the administration of thyroid to both humans and dogs

However, unusual amplitude of the *T* wave is by no means constant in hyperthyroidism, and White and Aub[107] found only a limited parallelism between the height of the *T* wave and the basal metabolism. Likewise, Rose, Wood and Margolies[96] found that the *T* waves in hyperthyroidism are not characteristically larger than normal and that they do not necessarily become reduced in size when the hyperthyroidism, is relieved. The *P* wave may be of unusual amplitude and duration in Graves' disease, the amplitude was above 3 mm. in 37 per cent of Parkinson and Cookson's patients. The electrical axis was normal in 77 of Parkinson and Cookson's 124 cases of Graves' disease, rotated to the left in 33, and to the right in 13. Rose and his associates observed that after thyroidectomy the electrical axis shifts to the left in about one-half the cases. The cause of this phenomenon was obscure, it was apparently not solely a result of gain in weight with upward displacement of the diaphragm.

In good accord with other evidences that hyperthyroidism generally causes little injury to the heart for long periods, if at all, is the usual paucity of the electrocardiographic changes bespeaking myocardial damage. It is true that Goodal and Rogers[38] described prolongation of the *P–R* interval in 242 of 787 cases of Graves' disease, but an equal incidence of impaired auriculo-ventricular conduction has not been reported by other investigators and has been rare in my experience. Davis and Smith[22] observed 6 cases of complete heart block in hyperthyroidism, but in 4 it followed acute infections and in 2 it was due to the action of digitalis on a previously damaged bundle. The possibility that the decreased glycogen content of the heart muscle may increase its vulnerability to toxic damage has been mentioned. Nevertheless, while abnormalities of the *Q–R–S* complex, *S–T* interval or *T* wave indicating myocardial damage may occur in hyperthyroidism (see Rose, Wood and Margolies[96] for details), they are rare in the absence of complicating coronary arteriosclerosis.

Circulatory Measurements.—The *arterial pressure* is played upon by several influences The increased output of the heart tends to elevate both the systolic and, to a less extent, the diastolic pressure. The same is true of the augmentation in circulating blood volume. The shortening of diastole due to the tachycardia interferes with the emptying of the arteries and thus tends to elevate the diastolic pressure. On the other hand, there is vasodilatation, evidenced by warm flushed skin and frequent capillary pulsation, which tends to depress the diastolic pressure. The resultant of these factors, as shown by comparison with the findings after the patient is up and about following thyroidectomy, is usually moderate elevation of the systolic pressure and little change or a depression of the

diastolic pressure, with resultant increase in pulse pressure.* Such figures as 130/70 mm. are common in young women of a constitutional type in which one ordinarily encounters a systolic pressure of about 100 mm Lerman and Means[62] found that the pulse pressure tends to be higher and the pulse rate slower in the male, the two mechanisms thus being correlated to bring about similar changes in cardiac output in both sexes. During thyroid crises the pulse pressure may be very great; such readings by the auscultatory method as 200/0 mm. are occasionally encountered. In older patients the blood pressure may be affected by complication with severe arteriosclerosis of the large vessels, which tends to raise the systolic and lower the diastolic pressure. In other middle-aged or old sufferers from Graves' disease there is, as described by Boas and Shapiro,[13] diastolic hypertension, which is presumably a manifestation of complication by essential hypertension.

The *venous pressure* is within normal limits as long as heart failure is absent.

As would be anticipated from the great increase in cardiac output, the *velocity of blood flow* is greatly enhanced in active hyperthyroidism. Using the radium C method, Blumgart, Gargill and Gilligan[8] found that the speed of blood flow through the lungs averages 83 per cent and that from the arm to the heart 34 per cent above the normal In a general way they found that the velocity of blood flow through the lungs parallels the basal metabolic rate and returns toward normal as the latter is lowered by iodine or thyroidectomy. With the decholin method, Tarr, Oppenheimer and Sager[103] found that the arm-to-tongue circulation time in Graves' disease averages nine seconds, in contrast to their normal of thirteen seconds. Similar figures are obtained with saccharin, with which, in very severe hyperthyroidism, the arm-to-tongue circulation time may be only six seconds.

The *circulating blood volume* is increased in Graves' disease. Using the carbon monoxide method, Chang[62] found that the circulating blood volume is above normal, in one case as much as 30.4 per cent, and falls after the administration of iodine or thyroidectomy. These findings have been confirmed with dye methods by Goldbloom and Libin[36] and Gibson and Harris.[33] The latter investigators state that there is a linear relationship between increase in blood volume and metabolic rate in hyperthyroidism. Chang found the *oxygen capacity* of the blood within normal limits, which accords with the evidence of the normal or diminished arteriovenous difference

* Under strictly basal conditions, Fullerton and Harrop[31] find little change in the arterial pressure in hyperthyroidism. The statements made in the text regarding the blood pressure apply under usual conditions of clinical work. In severe hyperthyroidism there is often an elevation of pulse pressure even under strictly basal conditions

(page 561) that the greater oxygen delivery to the tissues is accomplished entirely by augmentation of blood flow.

The *vital capacity* is usually depressed in active Graves' disease (Rabinowitch[58]), but there is no close inverse relationship between the metabolic rate and the vital capacity (Lemon and Moersch,[60] Blumgart[9] *et al.*). The diminution in vital capacity is not due to pulmonary engorgement, for the lung fields may be unusually clear in the roentgenogram. The muscular asthenia which is so cardinal a manifestation of Graves' disease may be responsible for the diminution in vital capacity, which is not extreme or constant.

The cardiac output has already been discussed.

Parenthetically, it may be remarked that certain of the circulatory measurements—tachycardia, increased cardiac output, accelerated velocity of blood flow, and greater circulating blood volume—bespeak the similarity of the circulation in a resting individual with Graves' disease to that of a healthy person during exercise. The circulation in Graves' disease is confronted by the same task as would be that of a healthy individual if he were to walk briskly through all twenty-four hours day after day; even during sleep, the circulation of the hyperthyroid person slows down relatively little.

Occurrence and Mechanism of Heart Failure in Hyperthyroidism.—In the foregoing we have seen the enormous burden that active hyperthyroidism throws on the heart, which pumps blood as though the individual were walking rapidly all day long Nevertheless, the heart may perform this increased work for many years and show no evidence of cardiac failure throughout the course of the disease. In the maximal hyperthyroidism of the thyroid crisis, the heart, even though beating at an uncountable rate, generally holds out and neither pulmonic nor systemic venous congestion appear to the end. Formerly, the frequency of heart failure in hyperthyroidism was overestimated. This was largely due to the evaluation of dyspnea, palpitation, and cardiac pain as symptoms of heart failure. But we have seen that these three symptoms often result from hyperthyroidism *per se*, without the participation of heart failure in their pathogenesis. Prior to the rise of thyroid surgery, large goiters compressing the trachea and great veins were common and some of the resulting symptoms mistakenly attributed to cardiac insufficiency. Doubtless, also, the actual incidence of heart failure in hyperthyroidism is now much less than formerly because thyroidectomy is performed in most cases before they go on to cardiac insufficiency.

Heart failure due to Graves' disease alone is almost unknown before the age of twenty and rare before forty years. Above the latter age the incidence steadily rises. Andrus[2] found that on entering the hospital heart failure was present in 23 of 158 cases

of exophthalmic goiter and 14 of 42 patients with adenomatous goiter with hyperthyroidism The rarity of heart failure due to hyperthyroidism alone before forty years is shown by the fact that of the 128 of Andrus' cases under that age, heart failure was present in only 9, and of these 6 also had rheumatic and 1 syphilitic heart disease, *i e*, in only 2 of 128 cases of Graves' disease under forty years did the heart fail as a result of hyperthyroidism *per se*. Kepler and Barnes[55] found severe heart failure with cardiac edema in 27 of 178 fatal cases of hyperthyroidism, but in 18 of these 27 there was also hypertension or intrinsic disease of the heart. Twenty-five of Kepler and Barnes' patients were under the age of thirty-five years, only one of these developed heart failure as a result of the hyperthyroidism alone and another because of hypertensive nephritis and hyperthyroidism

Two mechanisms of heart failure in Graves' disease are to be differentiated·

1 Cases in which the heart failure is evoked by both hyperthyroidism and another factor, notably hypertension, coronary arteriosclerosis, or rheumatic or syphilitic heart disease. The great importance of the thyroid factor in these patients is often shown by the prompt improvement of the heart that usually follows subtotal thyroidectomy or even pre-operative preparation with iodine despite the fact that the hypertension or other complication persists

2 Cases in which cardiac failure is due to hyperthyroidism alone. Here the heart generally returns to normal following successful thyroidectomy or, if the patient succumbs, postmortem examination reveals no cause for heart failure other than hyperthyroidism. Of the factors determining the incidence of heart failure in uncomplicated hyperthyroidism, advancing years seems to be by far the most important, as shown by the statistics cited above, the heart rarely gives way as a result of hyperthyroidism alone before the age of forty years In individuals of less than thirty years, one rarely sees heart failure as a result of uncomplicated Graves' disease even if the latter lasts several years. But in older persons the longer Graves' disease lasts, the greater seems to be the liability to cardiac failure. This point is not easy to support with convincing statistics because nowadays few persons are permitted to go on with active hyperthyroidism for long periods without surgical intervention. However, Andrus found that in exophthalmic goiter the average duration of symptoms of hyperthyroidism was 12.6 months in those without heart failure and over twenty-one months in those with failure, in his cases of adenomatous goiter the corresponding figures were sixteen months in those without failure and twenty-eight months in those with failure In most of the cases of heart failure in hyperthyroidism that I have seen there has been good evidence of the existence of active hyperthyroidism for several years. The

relationship of the severity of hyperthyroidism to the precipitation of heart failure is questionable. In young subjects even the maximal hyperthyroidism of the thyroid crisis does not usually lead to heart failure. On the other hand, in the elderly, moderate hyperthyroidism, such as documented by a metabolic rate of about plus 25 per cent, may result in heart failure, the proof of the connection being the improvement following thyroidectomy.

Much remains to be learned about how hyperthyroidism produces heart failure. The anatomical findings cited above show that even with severe cardiac failure the hyperthyroid heart generally reveals no lesions sufficient to explain the cardiac failure; in fact, the histological findings may differ in no way from those present in individuals without circulatory insufficiency. The most plausible explanation of the heart failure in Graves' disease would seem to be that it is a form of fatigue of the heart muscle brought on by long-continued overwork and diminution in the rest period due to the tachycardia. In excellent accord with this conception is the finding of De Fauw,[23] Andrus[2] and others that the glycogen content of heart muscle is decreased or exhausted in experimental hyperthyroidism.* That such fatigue of the heart muscle should occur far more readily in the elderly than in the young is readily comprehensible. Furthermore, the inevitable coronary arteriosclerosis of advancing years, even though it does not sensibly narrow the coronary lumens, may interfere with the delivery to the myocardium of the increased blood supply that is doubtless necessary in Graves' disease.

In the large majority of instances, hyperthyroidism produces heart failure through the intermediacy of auricular fibrillation. In the absence of hypertension or other complication, the thyroid heart rarely fails as long as the rhythm is regular. The frequency with which hyperthyroidism produces auricular fibrillation is noteworthy. Anderson[1] found that between 6 and 8 per cent of cases of Graves' disease have auricular fibrillation. Before the age of thirty years, auricular fibrillation is rare in Graves' disease and almost always paroxysmal. After that age, the incidence mounts with each decade so that 50 per cent of Magee and Smith's[71] cases in the eighth decade had complete arrhythmia. Fibrillation of the auricles due to hyperthyroidism is more often paroxysmal than when the arrhythmia arises from other causes, 23 per cent of Barker, Bohning and Wilson's[4] cases were transient or paroxysmal. Not rarely, auricular fibrillation, usually transient, first appears

* The poverty of the heart muscle in glycogen may well increase its susceptibility to infectious toxic injury, and is perhaps the basis of the 6 cases of complete heart block following acute infections in patients with Graves' disease reported by Davis and Smith.[22] In an instance of complete heart block in hyperthyroidism observed by Steuer,[101] the defect of conduction disappeared during iodine treatment. Since there was no evidence of infection, it was apparently a direct result of the hyperthyroidism.

after thyroidectomy. How hyperthyroidism produces auricular fibrillation is obscure, and probably will remain so until more is known of the pathogenesis of fibrillation of the auricles in general However, that the underlying changes are reversible is shown by the frequently paroxysmal nature of the arrhythmia and the usual return to regular rhythm following thyroidectomy.

While, as just mentioned, auricular fibrillation is concerned in the causation of almost all instances of failure of the thyroid heart, significant cardiac failure does not always result from complete arrhythmia in Graves' disease Some of the patients have no cardiac symptoms or only such complaints as palpitation or consciousness of irregular beat. Barker, Bohning and Wilson found high-grade heart failure in only 17 per cent and a slight grade of failure in 46 per cent of their patients with auricular fibrillation of thyrogenic origin, one-half of those with auricular fibrillation who died had cardiac failure

Far more rarely than auricular fibrillation, hyperthyroidism produces auricular flutter.

Little need be said concerning the symptomatology of heart failure in hyperthyroidism Dyspnea, cyanosis, swelling of the systemic veins and liver, edema and the other manifestations of failure of the left and right sides of the heart occur. The heart becomes enlarged Gallop rhythm is rare. To some extent the symptomatology of the heart failure is modified by the fact that it occurs on the terrain of an accelerated circulation. In consequence, the hands are often not as cold as might be anticipated from the other evidences of circulatory failure While the cardiac output is doubtless usually decreased below its previous level, Ewig and Hinsberg[27] and Grassmann and Herzog[43] have found that in hyperthyroidism classical symptoms of heart failure may be present despite a cardiac output that is above the normal (page 45). Similarly, Tarr, Oppenheimer and Sager[108] showed that the velocity of blood flow is not slowed as much in heart failure due to hyperthyroidism as in other varieties of cardiac insufficiency. In some cases, as pointed out by Levine and Sturgis[84] and others, the cardiac symptoms may so dominate the clinical picture of Graves' disease that the existence of the latter is not certain until the basal metabolism is determined ("masked hyperthyroidism"). Indeed, Barker, Bohning and Wilson have reported cases in which they believe that auricular fibrillation and flutter resulted from Graves' disease without elevation of the basal metabolic rate and in which the rhythm returned to normal following thyroidectomy. In all instances of auricular fibrillation of obscure origin, the possibility of Graves' disease should be borne in mind.

Anemia.—In severe anemia all the chambers of the heart are subject to enhanced strain, which may lead to dilatation and hyper-

trophy but only rarely to pronounced manifestations of cardiac failure or angina pectoris.

Accommodation of the Circulation in Anemia.—In many instances of severe anemia oxygen consumption is close to the usual (see Du Bois[24] for details), although in others it is definitely elevated (Richards and Strauss[94]). It is therefore evident that the circulation carries out its primordial function of oxygen transport despite the handicap of the diminished oxygen carrying capacity of the blood. This is accomplished through two mechanisms:

1. Utilization of a higher percentage of the arterial oxygen during each circuit of the blood. At rest in health only about 5 of the 18 volumes per cent of oxygen contained in the arterial blood are delivered to the tissues. The 13 volumes per cent remaining in the venous blood constitute a reserve of oxygen which can be impinged upon by the utilization of a higher proportion of the arterial oxygen. This reserve of oxygen is called upon by the healthy person during muscular exercise, when about twice as high a proportion of the arterial oxygen may be utilized, and is also used to atone for the diminished oxygen content of the arterial blood in anemia. However, the extent to which this mechanism functions is limited by the fact that as the mean oxygen content of the blood in the capillaries diminishes as a result of high percentage utilization, the oxygen pressure falls so sharply that the delivery of the gas to the tissues is greatly retarded. Moreover, since with normal cardiac output and oxygen consumption the tissues require 5 volumes per cent of oxygen, which corresponds to the entire oxygen capacity of blood with hemoglobin content of about 30 per cent, when anemia passes this severity even complete utilization of the oxygen of the arterial blood would not satisfy the oxygen requirements of the body. Regarding the cause of the augmented percentage utilization of the arterial oxygen in anemia, Liljestrand and Stenstroem[68] attribute it to an increase in the surface available for gas exchange due to the capillary dilatation that Krogh has shown to follow oxygen want. Another factor of quantitative significance still to be determined is that of increase in the average hydrogen-ion concentration of the capillary blood, which favors the liberation of oxygen from oxyhemoglobin. Barr and Peters[5] showed that in anemia the venous blood is more acid in relation to the arterial blood than in health. This difference is apparently due to diminution in the buffering power of the blood because of smaller hemoglobin content, as a result of which the carbon dioxide entering the blood from the tissues renders it more acid. However, the data of Richards and Strauss indicate that this factor is quantitatively not very important.

2. Increase in the minute volume of the heart. As just indicated, this mechanism is of necessity called upon when the hemoglobin

content of the blood falls below 30 per cent, but also functions with less severe degrees of anemia Plesch,[83] Liljestrand and Stenstroem, Richards and Strauss, and Dautrebande[21] have shown that in anemia the cardiac output rises as the hemoglobin falls. By bleeding dogs, Blalock and Harrison[6] have also demonstrated the inverse relationship between hemoglobin content and cardiac output. In very severe anemia the cardiac output may be more than double the normal. As a result of the greater cardiac output the arteriovenous oxygen difference falls, despite the above-mentioned fact that the proportion of the arterial oxygen utilized is greater than the normal 30 per cent.

How anemia calls forth greater cardiac output remains to be investigated. Dilatation of the small vessels due to oxygen want may be the initial link in the chain The lessened viscosity of the blood perhaps facilitates the more rapid blood flow.

Nor is much data available regarding the correlation of the two mechanisms of higher percentage utilization of the arterial oxygen and greater cardiac output in the compensation of anemia. The observations of Dautrebande indicate that increase in percentage utilization is the more important mechanism in relatively slight anemia, while as the hemoglobin falls further below 50 per cent the comparative significance of increase in cardiac output becomes progressively greater However, measurements by Liljestrand and Stenstroem and Richards and Strauss show considerable increase in cardiac output in even lesser degrees of anemia.

In accord with the greater cardiac output, Blumgart, Gargill and Gilligan[9] found in pernicious anemia and in secondary anemia not due to carcinoma an increase in the velocity of blood flow through the lungs inversely proportional to the hemoglobin content of the blood The velocity of flow is probably the more accelerated because of the diminution in circulating blood volume due to the small red cell volume. (See equation on page 54.) Blumgart and his associates did not find the velocity of blood flow accelerated in carcinomatous anemia, which they correlated with frequent evidences of cardiac failure in such patients I have not been impressed by the frequency of heart failure in carcinomatous anemia. It is also possible that the cachexia of carcinomatous patients may be accompanied by lowering of metabolic rate, which would entail diminution in cardiac output and consequently retardation in the velocity of blood flow

Another, though as yet unproved, mechanism which may help to compensate for anemia is diversion of blood from inactive to active organs Such a conception is supported by the observation of Fahr and Ranzone[29] that the capillaries of the skin are contracted in severe anemia.

The Heart in Anemia.—Severe anemia adversely affects the heart in two ways: (1) The maintenance of a greater cardiac output augments the work of the heart, and (2) the oxygen delivery to the heart muscle is diminished to such extent as the greater volume of blood flow and higher percentage utilization of the oxygen contained in the arterial blood fail to compensate for the anemia. Even relatively small oxygen want handicaps the heart, especially when it is performing increased work, and is probably responsible for the accumulation of fat in the heart muscle that is often prominent in anemia

In view of these two influences, it is not surprising that protracted anemia in other than cachectic individuals leads to hypertrophy and dilatation of the heart. To be sure, marked cardiac enlargement due to anemia is not nearly as common now as was formerly the case. This is due to the liver treatment of pernicious anemia and the mysterious decrease in the incidence of chlorosis, the two diseases which in a previous generation often caused severe anemia of long duration without cachexia In 23 necropsies in pernicious anemia, Cabot[18] found the heart hypertrophied 22 times; the heaviest heart weighed 710 grams in the absence of cause for hypertrophy other than anemia. Similar findings are recorded by others and pronounced dilatation is also present The hypertrophy and dilatation due to anemia involve all the chambers.

Enlargement of the heart resulting from anemia may be sufficiently pronounced to be detected by physical examination Roentgen examination then usually reveals enlargement of all the chambers. As pointed out by Kraus[57] and Goldstein and Boas,[37] prominence of the pulmonary conus of the right ventricle may lead to "mitralization" on dorso-ventral illumination The enlargement of the heart may recede quickly when the anemia improves, this occurs with especial rapidity during the liver treatment of pernicious anemia, and formerly was often seen as a result of the administration of iron in chlorosis (Gautier[32]). Functional systolic murmurs are the rule. Long-standing and severe anemia is also the condition in which functional diastolic murmurs are most often heard. Kraus detected such functional diastolic murmurs in 8 of 47 patients with pernicious anemia and Goldstein and Boas in 6 of 39 cases. The diastolic murmur is usually heard best in the third and fourth interspaces to the left of the sternum and presumably is due to aortic regurgitation produced by dilatation of the myocardium about the aortic ring (page 405) Goldstein and Boas heard a rumbling presystolic sound in 3 of their patients with pernicious anemia. This may have been an auricular sound resulting from the powerful auricular systole necessitated by the large stroke volume, similar sounds are sometimes heard in hyperthyroidism.

Despite the evidence of cardiac strain in the form of hypertrophy

and dilatation of the heart, anemia *per se* rarely leads to pronounced heart failure with venous engorgement of either the pulmonary or systemic circulation. This is perhaps largely due to the weakness and other symptoms of the patients, which usually keep them at rest. Exceptionally, pulmonary engorgement and swelling of the systemic veins and liver develop, and their connection with the anemia is proved by the improvement on improvement of the blood (liver treatment in pernicious anemia, cessation of uterine bleeding due to fibroids, etc.) It should be remembered that anemia itself can produce manifestations which simulate those of heart failure. Thus, edema of the lower extremities and puffiness of the face is common in anemia, and I have several times satisfied myself that it was not due to heart failure by finding normal venous pressure. Factors which may be concerned in the pathogenesis of anemic edema are increased permeability to protein of the capillary walls due to oxygen want and depression in the protein content of the plasma, the latter of which is not uncommon in various forms of anemia Exertional dyspnea is a banal symptom of anemia, which may occur without pulmonary engorgement and in the presence of normal circulation time and venous pressure; it is to be regarded as a direct manifestation of the anemia. The liver is often palpably enlarged in pernicious and other forms of anemia without heart failure

As pointed out by Herrick and Nuzum,[45] anemia may precipitate *cardiac pain*. The latter may occur in either pernicious or secondary anemia. Anginal pain was mentioned in 43 of 1560 histories of cases of pernicious anemia reviewed by Willius and Giffin.[110] Specific questioning elicits a much higher incidence of cardiac pain in severe anemia Thus, Pickering and Wayne[84] found that of 25 consecutive patients with severe anemia, 8 complained of cardiac pain induced only by exercise and relieved by rest. In 6 of these individuals they were able to call forth the pain by having the patient exercise. The pathogenetic rôle of the anemia is demonstrated by the cessation of the pain when the hemoglobin rises It is probable that in most cases, as in one studied at necropsy by Herrick, there is an underlying basis of coronary arteriosclerosis, and the anemia is merely the precipitating factor. However, in a case studied at necropsy by Willius and Giffin, though apparently not in detail, coronary arteriosclerosis was absent. Especially with pre-existent coronary narrowing, anemia may produce inadequacy of the blood supply to the heart and consequent anginal pain through at least four mechanisms: (1) The maintenance of increased cardiac output increases the work of the heart and consequently the volume of blood flow needed; (2) more blood flow is needed to supply the hypertrophied myocardium; (3) the anemia directly favors oxygen want in the myocardium; (4) Pickering and Wayne found a ten-

dency in severe anemia to decreased mean arterial pressure and increased pulse rate, the former of which hampers coronary filling and the latter of which abbreviates the rest period of the heart. Interestingly enough, Pickering and Wayne found that severely anemic patients not uncommonly have intermittent claudication in the extremities, the pathogenesis of which is presumably similar to that of the angina pectoris.

Arteriovenous Fistula.—A variety of heart failure of interest far transcending its frequency is that resulting from arteriovenous fistula (aneurysm). It is the outcome of strain on all the chambers of the heart produced by increase in the venous return and consequently in the cardiac output Though rare in time of peace, recognition of the effects of arteriovenous fistula on the heart is important, for surgical closure is quickly followed by disappearance of the general circulatory manifestations Matas and Heninger[74] have observed the same type of circulatory disturbance in a patient with congenital cavernous hemangioma, cure followed surgical removal The alterations in the circulation due to arteriovenous fistula acquire added interest from their close resemblance to those of aortic regurgitation The abnormalities common to the two conditions are those resulting from the rapid leakage of blood from the arterial system and the increased output of the left ventricle The differences, apart from the local signs, are due to the fact that in the one case the leakage is into a vein so that the work of the whole heart is augmented, while in the other the leakage is directly into the left ventricle so that, until this chamber fails, only the left side of the heart is implicated

The local manifestations of arteriovenous fistula (pulsating tumor, machinery murmur louder in systole, purring thrill, venous engorgement near the fistula, diminished arterial pulsation and perhaps edema distal to the fistula) will not be discussed here The effects of the fistula on the general circulation—which are the more pronounced the larger the fistula and the artery involved and the closer to the heart it is located—are as follows:

General Circulatory Manifestations of Arteriovenous Fistula—1. Corrigan pulse and increased pulse pressure The pulse resembles that of aortic regurgitation (page 469) in its rapid, jerking rise and collapsing fall These palpatory findings correspond to an increased pulse pressure. The latter is due almost entirely to depression of the diastolic pressure; the systolic pressure usually is little changed. Figures of the order of 125/40 mm. are most common, but the diastolic pressure by the auscultatory method may approach zero The fall in diastolic pressure is due almost entirely, if not completely, to leakage of blood through the fistula, and the diastolic pressure generally returns to normal when fistula is closed. Lewis[65] and Ellis and Weiss[25] have found evidence of widespread arteriolar

dilatation in arteriovenous aneurysm (capillary pulsation is often present), but this is probably only a subsidiary factor in depressing diastolic pressure Lewis and Drury[66] noted that, like in aortic regurgitation, the pressure in the lower extremities is much higher than in the upper (page 471)

2 One would anticipate that the *cardiac output* in arteriovenous fistula is increased by the volume of blood that passes through the abnormal communication For prior to the development of heart failure there is no indication of decrease in blood flow through any part of the body and the patients are capable of hard work. In order that blood flow through the rest of the body be normal, cardiac output must be increased by the amount of the leak This amount may be very considerable, Lewis and Drury estimate that in a large communication between one-fifth and one-half the cardiac output may pass through the fistula. While Lewis and Drury did not believe that the cardiac output is augmented in arteriovenous fistula, Harrison, Dock and Holman[41] demonstrated directly that there is a very pronounced increase They produced an arteriovenous communication in a dog and found that the cardiac output rose approximately 100 per cent. In a patient with arteriovenous fistula, Smith[99] found that the cardiac output decreased 58 per cent following surgical closure of the communication. While the carbon dioxide method used by Smith does not give accurate absolute figures, the comparative results are probably significant Indeed, the cardiac output before closure of the fistula was doubtless proportionately even higher, for a reason to be mentioned in conjunction with the findings of Weiss and Ellis. These investigators found only a small decrease in cardiac output in one patient following ligation of an arteriovenous aneurysm. However, inasmuch as they used the acetylene method for measuring cardiac output, it would seem that they did not measure the blood passing through the fistula, which must have returned to the lungs before the end of the rebreathing period (page 37). Ellis and Weiss' finding is thus good evidence that the cardiac output is increased in arteriovenous aneurysm

3 *Enlargement of the heart* due to hypertrophy and dilatation In all 5 of Lewis and Drury's cases, the orthodiagram showed the dimensions of the heart at the upper limit of normal or beyond The enlargement may attain very considerable degree and involves all the chambers, the hypertrophy of the right ventricle is usually especially pronounced and results in a globular appearance of the heart With closure of the fistula, the heart diminishes in size; in the case of Hitzig and Master[47] the transverse diameter before operation was 15.3 cm and five months after operation 13 cm Reid[82] observed enlargement of the heart of the dog following experimental arteriovenous fistula. The hypertrophy and dilatation of the heart, involving all the chambers, is doubtless primarily

a result of the greater work performed by the organ in mastering the larger venous return But the depression of the mean aortic pressure may also be concerned in the production of the dilatation through the intermediacy of deficient coronary flow (see below).

4. There is usually a moderate acceleration in the rate of the heart Lewis and Drury attribute the tachycardia to a vagal reflex initiated by the fall in mean arterial pressure, i e, to the reflex mechanism now known to be initiated by the receptors in the carotid sinus and aorta The absence of substantial rise in venous pressure despite greater venous return is presumably explained by the increased work of the heart.

An interesting and sometimes diagnostically important phenomenon is the slowing of the pulse on compression of an arteriovenous aneurysm—the bradycardiac reaction described by Nicoladoni[80] and Branham[15] The pulse rate often falls from 90 to 60 or less per minute The mechanism of the bradycardia reaction is not clear Lewis and Drury believe it to be a reflex vagal slowing produced by the rise in arterial pressure that results from compression of the aneurysm, they observed that the reaction no longer occurs after atropinization, but this has been disputed (Hitzig and Master). It is possible that the decrease in the venous return to the heart that doubtless follows compression of the aneurysm may slow the heart through the mechanism of the Bainbridge reflex.

5. In experimental arteriovenous fistula Holman[49] found an increase in the circulating blood volume This was not present in a patient studied by Ellis and Weiss The increase in circulating blood volume, when present, is doubtless correlated with the greater cardiac output, which it also accompanies under such circumstances as exercise and excitement (page 61), as well as in hyperthyroidism (page 570).

Heart Failure in Arteriovenous Fistula.—In view of the strain thrown on the heart by the increased venous return, it is not surprising that cardiac failure develops sooner or later in a high proportion of the cases. Another factor which is probably important in the genesis of heart failure is diminished coronary flow due to the lowering of the mean aortic pressure The factor of diminished coronary flow becomes more significant as the mass of the heart muscle increases with longer duration of the fistula with its constant strain on the heart The aneurysm may be present for many years before heart failure becomes manifest—fifteen and nineteen years in the cases of Osler.[81] On the other hand, the patient studied by Hitzig and Master had symptoms of heart failure within two years of the production of a popliteal arteriovenous communication, and the interval may be even shorter The symptoms are usually those of both left- and right-sided failure—dyspnea, pulmonary engorgement, swelling of the systemic veins and liver, and edema In some cases the symptoms of right-sided failure predominate.

Thus, Hoover and Beams[51] noted that in their patient, who was tapped 40 times in two years for ascites due to heart failure, engorgement of the lungs was absent. In such cases it is to be presumed that the failure of the right ventricle so reduces pulmonary blood flow that it is within the functional capacity of the left ventricle. On the other hand, there are also cases of arteriovenous communication with isolated failure of the left side of the heart. An excellent example is the patient studied by Hitzig and Master, whose symptoms were those of left-sided failure with prolongation of the arm-to-tongue circulation time in the presence of normal venous pressure. The pathogenesis of isolated left-sided failure in arteriovenous communication is not clear; possibly, but purely hypothetically, it is due to the thicker left ventricle suffering from diminished coronary flow more than does the right ventricle. Anginal pain which disappeared after closure of an arteriovenous fistula was observed by Perthes.[83]

Heart failure due to arteriovenous aneurysm may last for years, but tends to progress and leads to death unless the fistula is closed. Then, the relief is spectacular. Leriche[61] noted that following the application of the clamp the patient became less dyspneic and the swollen liver had receded greatly before the operation was finished. Hitzig and Master found that the arm-to-tongue circulation time, which was twenty-eight seconds pre-operatively, had returned to a normal value of 13.5 seconds in less than twenty hours after the operation. Even during compression of the aneurysm dyspnea and other symptoms of heart failure may be much ameliorated, and Hitzig and Master observed that the arm-to-tongue circulation time was shortened seven seconds. In no other form of heart failure is equally rapid relief to be obtained.

Hypoglycemia.—A remarkable variety of cardiac strain, which may lead to heart failure or more often angina pectoris, is that resulting from overdosage of insulin. Serious episodes of this nature apparently occur only in those with previously damaged hearts. The available evidence indicates that both increase in cardiac work due to circulatory acceleration and decrease in the functional capacity of the heart are concerned in the pathogenesis of the cardiac strain.

The circulatory manifestations of hypoglycemia were originally observed as a result of unintended overdosage with insulin in diabetics, but are now encountered much more strikingly in the insulin shock treatment of psychoses (*cf.* Messinger[76]).

The Circulation in Hypoglycemia.—Simple clinical observation often reveals that hypoglycemia is accompanied by dilatation of the small vessels and acceleration of the circulation. The flushed skin and warm extremities—in blatant contrast to the cold pallor of acidotic intoxication—bespeak increased cutaneous blood flow. Peripheral dilatation is also indicated by the capillary pulsation

which was present in 12 of Ernstene and Altschule's[26] 13 cases. Since oxygen consumption is increased rather than decreased in hypoglycemia, the bright red color and high oxygen content of the venous blood observed by Holzer and Klein[50] and Wiechmann and Koch[108] also evince more rapid blood flow. The pulse rate is accelerated. Wilder[109] observed that the systolic pressure may be considerably elevated during insulin reactions. Ernstene and Altschule found an average increase in pulse pressure of 73 per cent, which was due to fall in diastolic and usually rise in systolic tension. The direct proof of the circulatory acceleration indicated by these findings has been furnished by the demonstration of Lauter and Baumann[59] with the ethyl iodide method and Ernstene and Altschule with the more correct acetylene method than the minute volume of the heart is augmented during hypoglycemia. The last-named investigators found an average increase of 29 per cent and a maximal rise of 86 per cent in cardiac output According to Lauter and Baumann, the increase in cardiac output may last for several hours after hypoglycemia has been relieved by the administration of glucose.*

The circulatory acceleration of hypoglycemia has been regarded as a compensatory response to glucose want in the tissues, just as oxygen deficiency increases the blood flow. But such a teleological, and purely theoretical, conception does not explain the mechanism through which the circulatory acceleration is evoked It is plausible, though as yet unproved, that this occurs through the intermediacy of enhanced secretion of epinephrin Cannon, McIver and Bliss[20] have adduced evidence that the injection of insulin leads to sympathetic stimulation and increased secretion of epinephrin The circulatory manifestations of hypoglycemia—accelerated heart rate, increased pulse pressure, enhanced cardiac output, and liability to angina pectoris in the presence of coronary sclerosis—are precisely those which would be expected from hypersecretion of epinephrin.

The Myocardium in Hypoglycemia.—There is also electrocardiographic evidence that the myocardium suffers during hypoglycemia Wittgenstein and Mendel,[111] Middleton and Oatway,[77] Haynal[44] and Lauter and Bauman have observed during hypoglycemia decrease in amplitude and negativity of the T wave, displacement of the R-T segment from the isoelectric level, and less often prolongation of the P-R interval. They have also produced these changes in the experimental animal by the injection of insulin. In individuals with previous coronary artery disease, extrasystoles and auricular fibrillation have been observed during hypoglycemia.

* The increase in cardiac output, rise in pulse pressure, and other evidences of circulatory acceleration show that insulin hypoglycemia does not produce circulatory shock (Chapter XXXII), so that, in this sense, the term "hypoglycemic shock" is a misnomer

Whether the myocardial damage documented by these changes is due to glucose deficiency in the heart muscle or is produced in some other way by overdosage of insulin remains to be determined.

Angina Pectoris and Heart Failure in Hypoglycemia.—That the increased cardiac work and deleterious effect of hypoglycemia on the myocardium should produce angina pectoris or heart failure in an individual with a previously healthy heart does not seem to have been observed, although palpitation may occur. But a high proportion of middle-aged and elderly diabetics receiving insulin have well-marked coronary arteriosclerosis, and in these overdosage of insulin may lead to serious cardiac manifestations and rarely even a fatal termination. Soon after the introduction of insulin, Gigon[34] mentioned briefly that a diabetic with "starker Kreislaufstoerung" died after the third injection of insulin. Since then, Hetenyi,[46] Turner,[104] and others have reported cases in which the injection of insulin was followed on repeated occasions by angina pectoris; in some of the patients it was demonstrated that the simultaneous administration of glucose prevents the angina. I have seen several cases in which great caution was needed in the administration of insulin because of anginal pain following the injections. Joslin[54] and Blotner[7] observed myocardial infarction soon after the administration of insulin and I have seen a similar accident. Von Noorden and Isaac[105] and others have observed a fatal outcome in diabetics with coronary sclerosis following the injection of insulin. Of course, the possibility of mere coincidence must be borne in mind, but this is evidently not always true. Much less frequent than cases with cardiac pain are those in which heart failure is precipitated in individuals with coronary sclerosis by the injection of insulin, and relieved when insulin is discontinued and glucose administered Nicely and Edmundson[79] and Reinwein[93] have each reported two such cases In these patients the edema is apt to be especially severe, perhaps because of the effect of insulin in favoring water retention under certain circumstances. It is obvious that great caution must be used in the administration of insulin to individuals with coronary artery disease.

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CHAPTER XXX

HEART FAILURE INITIATED BY GENERALIZED CARDIAC STRAIN: II. DIFFUSE MYOCARDIAL DISEASE

WIDESPREAD myocardial damage results from one of three general types of processes:

1. *Ischemic damage* to the heart muscle resulting from narrowing of the coronary arteries. Because of the greater susceptibility of the thick left ventricle to ischemic damage, heart failure due to coronary artery disease is almost always initiated as left ventricular failure, and is therefore considered in conjunction with the latter (page 411). An allied pathogenesis of functional impairment of the myocardium is that due to insufficient oxygen delivery due to changes in the composition of the blood (anemia, arterial anoxemia); it is exemplified by the frequency with which electrocardiographic changes occur in carbon monoxide poisoning (*cf.* Steinmann[33]).

2. *Myocarditis* of infectious etiology. By far the most important form of myocarditis is that due to rheumatic infection (page 338). However, the form of heart failure in rheumatic myocarditis is almost always determined by associated valvular defects of pericarditis, and it is therefore considered in conjunction with the latter. The other infection in which heart failure due to myocarditis may completely dominate the clinical picture is diphtheria, it is considered below. While myocarditis may occur in various other infections, most often it is not nearly so important in the clinical ensemble as is peripheral circulatory failure, with which it is discussed (Chapter XXXII).

That some instances of so-called congenital cardiac hypertrophy are due to diffuse myocarditis is mentioned on page 314 There are also extremely rare cases of acute isolated myocarditis (also known as Fiedler's myocarditis), the etiology of which is completely obscure The clinical picture is that of progressive heart failure lasting from a few weeks to over a year. Necropsy reveals that the cardiac failure is due to diffuse inflammatory disease of the myocardium with extensive interstitial infiltration (Scott and Saphir,[34] Simon and Wolpaw[35]) The doubtful significance of syphilitic myocarditis is mentioned on page 466.

3 *Regressive changes* in the heart muscle which are part of generalized metabolic disturbances, such as myxedema, beriberi, and von Gierke's glycogen disease (page 314).

THE DIPHTHERIA HEART

Next to rheumatic fever, diphtheria is the infectious disease complicated in the highest proportion of cases by heart failure. Diphtheria formerly ranked high among the causes of circulatory failure, but since the great success of the campaign for the prevention of the disease and the widespread and early use of the antitoxin, this cause of heart disease has been thrust statistically into the background and in New York City is now disappearing. Older estimates by Romberg[11] and others indicated that the circulation fails in between 10 and 20 per cent of cases of diphtheria, but I believe that a much lower incidence is observed at present in New York City, presumably because of the early and adequate use of the antitoxin.

In addition to the heart failure with which this section is concerned, it appears that diphtheria may also be complicated by peripheral circulatory failure. In some of the cases, the circulatory failure apparently results from both cardiac and peripheral damage. Little is known concerning the mechanism of peripheral circulatory failure and consequent deficient venous return to the heart in diphtheria Because of the great affinity of the exotoxin of the diphtheria bacillus for the peripheral nerves, it has been thought that damage to the vasomotor nerves may be the significant factor. Edmunds and Johnston[10] found evidence that the circulatory collapse is due to the effect of the exotoxin on the myoneural junction of the splanchnic nerves, with resultant increase in capacity and stagnation of blood in the vessels of the splanchnic area (page 662).

Pathological Anatomy of the Diphtheria Heart.—Cardiac failure in diphtheria finds an adequate explanation in the extensive myocardial lesions present at necropsy Experimental evidence indicates that these result from the direct action of the exotoxin on the muscle fibers At necropsy, the heart is dilated. Frequently, hemorrhages are seen under the epicardium and endocardium, less often in the midst of the heart muscle. On section, the latter appears cloudy and often pale, there may be grayish or yellowish spots and streaks Occasionally, mural thrombi are present. Endocarditis and pericarditis are rare, and presumably attributable to secondary infection. Microscopic examination in the cases with heart failure reveals severe lesions. In the cases that succumb in the early stages of the disease, these lesions consist almost entirely of degenerative changes in the muscle fibers ("parenchymatous myocarditis" of the older pathologists) and perhaps interstitial edema, with usually little interstitial cellular infiltration. The changes in the muscle fibers are variegated: necrosis, indicated by deficient staining of the muscle nuclei; loss of transverse striation; fatty, albuminous and vacuolar changes; and waxy transformation of the type of Zenker's degen-

eration in the skeletal muscle. These regressive changes may lead to extensive areas of destruction of the heart muscle. The fibers of the conduction system may be implicated very early, but are not always strikingly affected In cases which succumb after the second week, interstitial cellular infiltration becomes more prominent and areas of granulation tissue with resultant replacement fibrosis appear. In some instances, the interstitial infiltration becomes so marked that older investigators described the process as interstitial myocarditis, but the available evidence (Moenckeberg[29]) indicates strongly that the primary changes are in the muscle fibers, and that the cellular infiltration is at least predominantly secondary Widespread scarring and enlargement of the heart may remain as residues of healed diphtheritic myocarditis.

Clinical Pictures.—In malignant diphtheria, circulatory failure may appear in the first days. Such early circulatory failure is probably at least most often of peripheral genesis and not due to myocarditis. The common time for heart failure due to diphtheritic myocarditis to make its appearance is in the second or third week, when the temperature has fallen and convalescence seems to be progressing uneventfully There are also rare instances in which heart failure does not become manifest until two months after the onset of the disease, which may have seemed mild during the onset of the angina

Various clinical pictures are encountered Probably as a result of the rapid onset of the heart failure, the manifestations of decreased cardiac output dominate the symptomatology, the picture is that of "cardiac shock," closely simulating that of peripheral circulatory failure except for the accompanying evidences of engorgement of the lungs and systemic veins. Most feared and tragic of the consequences of the diphtheria heart is sudden death; the seemingly convalescent child sits up in bed and then falls pulseless However, such tragedies are rarely altogether unexpected if the pulse and other clinical features are followed carefully during convalescence. Common early indications of the onset of heart failure in diphtheria are pallor not due to anemia, loss of appetite, nausea, vomiting (an especially important symptom), abdominal pain, and lethargy Often, changes in the pulse signal the development of the circulatory disturbance before there are subjective symptoms Most frequently, the pulse is accelerated and may be irregular as a result of extrasystoles, auricular fibrillation or other disturbance in rhythm. Some of the tachycardias are perhaps attributable to diphtheritic neuritis of the vagus. Less common, but particularly grave, are those cases in which slowing of the pulse testifies to the existence of partial or complete auriculo-ventricular block.

The usual and frequently cadaveric pallor of the patients is especially noteworthy; it testifies eloquently to the small cardiac

output. The cardiac damage is revealed by enlargement of the heart, gallop rhythm, the above-mentioned arrhythmias and conduction disturbances, and by swelling of the liver which is often disproportionately more pronounced than the other evidences of cardiac weakness. Dyspnea, cyanosis and edema may all occur, but are often absent. The veins of the neck are generally distended and the venous pressure may be high. The arterial pressure is most often depressed, sometimes strikingly so. The urine is scanty and often albuminous. Rare manifestations are attacks of angina pectoris; hemiplegia, other paralyses, or gangrene of an extremity due to embolization of thrombi from the dilated left heart; and the Stokes-Adams syndrome in the cases with heart block. Heart failure may be accompanied by diphtheritic paralysis of the palate or other muscles. Bronchopneumonia is a common terminating complication.

The prognosis of circulatory failure in diphtheria is uncertain; according to Romberg, about one-third of the patients succumb. Sometimes, the cardiac failure is mild and transient, but in other cases it is severe and lasts for weeks or even months with alternating exacerbation and improvement. Sudden death may occur at any time, though more often the fatal outcome terminates progressive intensification in the circulatory failure for some days or weeks. Heart block is a particularly ominous sign. All 19 cases of complete heart block studied by Stechner[31] died; but others have reported survival of such patients, which I have also seen once. Of Stechner's 6 patients with delayed intraventricular conduction, 4 had electrocardiographic recovery.

The after-effects of diphtheria on the heart deserve further study. Jones and White[19] examined 100 individuals who had had severe diphtheria five to eight years previously, but none showed any evidence of heart disease. On the other hand, Hoskins[16] found that persistent electrocardiographic changes are quite common after diphtheria Butler and Levine[6] found that 10 of 20 individuals with heart block of obscure causation had a history of diphtheria, and believe this infection to be of etiological significance in a considerable proportion of such cases. The heart may remain permanently enlarged after diphtheritic myocarditis; persistent valvular defects have also been described on rare occasions, but their direct connection with infection by the Klebs-Loeffler bacillus remains to be established.

THE MYXEDEMA HEART

Like other bodily functions in myxedema and cretinism, cardiac action and blood flow are sluggish, the antithesis of the accelerated heart and circulation of hyperthyroidism. While the small cardiac accomplishment is probably primarily a consequence of the small demand for cardiac work by the quasi-hibernating organism, there

is also good evidence that the actual functional capacity of the heart is at least often diminished in hypothyroid states. In the severe forms of myxedema and cretinism, this is probably always the case. Moreover, in long-standing hypothyroidism, pronounced and precocious arteriosclerosis develops and may implicate the coronary arteries. Nevertheless, heart failure and angina pectoris are the exception and not the rule, a phenomenon which is doubtless a corollary of the small demands on the heart.

The Circulation in Myxedema.—As would be anticipated from the diminished oxygen consumption, the chief characteristic of the circulation in myxedema is a diminution in the volume of blood flow. The pronounced decrease in cardiac output in spontaneous myxedema was first demonstrated by Bock and Field (reported by Means[26]) and later by Bansi[3] and others. These observations showed that the administration of thyroid to myxedematous subjects is followed by a rise in cardiac output. The decrease in cardiac output in myxedema occurs despite the usual secondary anemia which would tend to accelerate blood flow. In 7 patients in whom the thyroid gland had been completely removed for therapeutic purposes, Altschule and Volk[1] found that the minute volume of circulation was greatly diminished; with the acetylene method, the cardiac output per square meter of body surface was only 1.1 to 1.4 liters per minute as contrasted with the normal value of 2.2 liters. The decrease in cardiac output was due to both bradycardia and diminution in output per beat. Altschule and Volk found that the cardiac output falls proportionately more than does the oxygen consumption, with the result that the arteriovenous difference rises. This finding harmonizes with the observation that in Graves' disease the cardiac output is increased relatively more than the oxygen consumption (page 561), and is perhaps a manifestation of relatively greater diminution in cutaneous blood flow, which serves to decrease heat loss and thus tends to maintain body temperature despite low heat production. The small cutaneous blood flow, which is evinced by the cold skin, may well be concerned in the production of certain of the changes in the skin and the falling out of the hair so characteristic of myxedema.

One manifestation of the diminished cardiac output is the slowing in the *velocity of blood flow* demonstrated by Blumgart, Gargill and Gilligan.[5] They found that the velocity of blood flow tends to parallel the basal metabolic rate and returns to normal as a result of the administration of thyroid. In myxedema, despite the absence of passive engorgement, the blood may flow as slowly as in pronounced heart failure; the arm-to-tongue circulation time may be double the normal (twenty-five seconds or longer with saccharin). In exceptional instances, despite a low metabolic rate, the circulation time is but little prolonged; further studies are needed to deter-

mine whether, in these cases, diminution in cardiac output is not due more to decrease in cross-section of the vascular bed resulting from smaller circulating blood volume than to slowing in the linear velocity of flow. Interestingly enough, Macy, Claiborne and Hurxthal[24] found that the velocity of blood flow is not decreased when the metabolic rate is lowered by hypopituitarism.

Another manifestation of myxedema which is presumably correlated with the decrease in cardiac output is the diminution in *circulating blood volume* found by Thompson.[41] In 9 patients with myxedema, he showed that the circulating plasma volume increased an average of 22.9 per cent on the administration of thyroid extract, with a slightly greater rise in the total circulating blood volume. Thompson's observations revealed a parallelism between the metabolic rate and the circulating plasma volume.

The *arterial pressure* is not constantly affected in myxedema. Most often, the systolic and diastolic pressures tend to be somewhat low and may rise after the administration of thyroid. In accord with the small stroke volume, the pulse pressure is usually small and increases as a result of thyroid medication. In exceptional instances (Fishberg[14] and Duden[9]), myxedema is accompanied by arterial hypertension. Most often, the association of hypertension and myxedema is probably fortuitous, but this does not seem to be always true; in Duden's case, the elevated blood pressure twice fell when thyroid was administered, to rise again when the medication was discontinued. In one of Ohler and Abramson's[30] cases the blood pressure fell from 180/120 mm. to 108/62 mm. under treatment. And the patient with myxedema and hypertension reported by the writer was only twenty-one years of age at the time of death, an age at which ordinary essential hypertension is a rarity.

The *venous pressure* is normal in myxedema without heart failure

The *vital capacity* was found by Blumgart, Gargill and Gilligan[5] to be strikingly diminished in myxedema, despite the absence of pulmonary engorgement. While not proved, it is possible that the decrease in vital capacity is part of the general muscular weakness, which has been demonstrated in the voluntary muscles by Rockwell (cited by Fahr). Contrary to the findings in spontaneous myxedema, Schnitker, Van Raalte and Cutler[32] observed little change in vital capacity in the hypothyroidism produced by total ablation of the thyroid gland.

The Heart in Myxedema.—The cardiac manifestations of high-grade myxedema were first described by Zondek,[44] who spoke of "myxedema heart." The important characteristics of the myxedema heart are as follows:

Enlargement —Comparison of the size of the heart in myxedematous subjects before and after the administration of thyroid generally reveals enlargement which diminishes or disappears under the medi-

cation. Ayman[2] and his associates find that of 22 cases reported in the literature, the average decrease in the transverse diameter of the heart after thyroid therapy was 3 3 cm., with a minimal decrease of 1 cm and a maximal of 6 3 cm. Of 30 patients with myxedema heart to whom Means and Lerman[27] administered thyroid, the transverse diameter decreased 2 to 7 cm in 14 and 1 to 2 cm. in 6. How great cardiac enlargement may result from myxedema is indicated by Fahr's[11] observation, in which the volume of the heart decreased by one-half under thyroid medication The enlargement involves all the chambers of the heart, and may be accompanied by pronounced increase in the transverse diameter of the vascular pedicle, which recedes on thyroid treatment (Ayman *et al*) Often the separation of the individual arcs of the cardiac borders is less distinct than normally Apparently, the only specific characteristic of the enlargement of the myxedema heart is that it recedes on the administration of thyroid but not of digitalis.

The cause of the enlargement of the myxedema heart has been repeatedly discussed but not unequivocally established. That the pronounced enlargement often present can be due to thickening of the walls of the heart by myxedematous swelling seems out of the question from the few available descriptions of the postmortem appearance of the heart in myxedema While pericardial effusion has been observed in rare instances (Gordon,[15] Marzullo and Franco[25]) and may exceed a liter, the roentgen appearance of the heart does not suggest that this is the usual cause of the enlargement A high position of the diaphragm may sometimes contribute to the broadening of the transverse diameter but is not always present In all probability, the enlargement is due to dilatation of the heart manifesting diminished functional capacity of the myocardium and a specific result of thyroid deficiency. The electrocardiographic changes described below indicate the deleterious effects of hypothyroidism on the myocardium. Felix[13] has found that the addition of thyroxin to the perfusion fluid increases the amplitude of contraction of the frog's heart. It seems a fair corollary, although one requiring direct proof, that lack of the thyroid hormone diminishes the capacity for work of the heart and thus favors dilatation. In some instances the protracted anemia may contribute to the dilatation

Sluggish Cardiac Action —In severe myxedema the rate of beat is generally, although not always, slowed· exceptionally, the basal pulse rate is in the forties despite absence of conduction disturbances Fluoroscopic observation may reveal sluggish cardiac contractions of small amplitude, the reverse of what is seen in Graves' disease The sluggish systole is probably responsible for the distant heart sounds often present.

Work.—Stewart[39] and his associates found by calculation from the observed cardiac output and arterial pressure that the work

performed by the heart in myxedema is low and not commensurate with the size of the heart.

Electrocardiographic Changes —The characteristic electrocardiographic picture of the myxedema heart, first depicted by Zondek, consists in diminished voltage of all the deflections with low or flat *P* waves, low *R* waves, and low, flat or inverted *T* waves Thacher[40] found the same changes in cretinism. The deflections increase in amplitude as a result of the administration of thyroid Ohler and Abramson found considerable parallelism between the metabolic rate and the height of the *R* wave, but in different cases they did not detect a constant relationship between the amplitude of the *R* wave and the metabolic rate In addition to the low amplitude of the deflections, prolongation of the *P–R* interval and changes in the *Q–R–S* complex, the *R–T* interval, and the direction of the *T* wave may result from myxedema, the connection being proved by the return to normal under the influence of thyroid therapy Partial and complete heart block clearing up on the administration of thyroid have been described (Luten,[23] Willius[41]) Fahr observed prolongation of the *Q–R–S* complex to 0.18 second, which diminished to 0.08 second under thyroid treatment.

The regression after thyroid administration shows that the electrocardiographic abnormalities of myxedema are specific manifestations of thyroid deficiency. But the precise nature of the changes in the heart muscle (myxedematous changes in the muscle fibers? myxedematous swelling of the connective tissue with compression of the muscle fibers?) is totally unknown. Lueg[22] attempted to explain the decreased voltage of the deflections as a result of augmented resistance in the skin. But this explanation fails to elucidate the other electrocardiographic changes, and is disproved by the finding of Coelho[8] that the same tracings are obtained with needle electrodes. Moreover, Ohler and Abramson found that increasing the resistance by poor contact with the skin increases rather than decreases the height of the complexes.

Heart Failure and Angina Pectoris in Myxedema.—The characteristics of the myxedema heart—enlargement, sluggish contraction, and electrocardiographic abnormalities—indicate that the functional capacity of the organ is diminished. Nevertheless, unequivocal evidences of cardiac failure are present in only a minority of instances of myxedema heart. It is true that Fahr observed 5 examples of severe and 8 of mild heart failure in 17 patients with myxedema. But other clinicians report a much lower incidence of heart failure Thus, Means and Lerman encountered frank cardiac insufficiency in only 1 of 30 patients with myxedema Cardiac failure was present in less than 30 per cent of the cases of myxedema heart collected from the literature by Ayman and his associates and in neither of the 2 patients they studied. In my experience

only a small minority of patients with severe myxedema have had evidences of cardiac insufficiency in the form of pulmonary or systemic venous engorgement And in some of these cases it seemed clear that the heart failure was not due to the myxedema directly but to coronary arteriosclerosis or rarely also hypertension It would seem that the rationale of the rarity of failure of the myxedema heart is that cardiac work is diminished to such an extent that it is within even the diminished functional capacity of the heart. This is the principle which has been applied by Blumgart in his treatment of heart failure by extirpation of the thyroid (page 743).

In the exceptional cases in which the myxedema heart fails, the clinical picture includes the usual manifestations of insufficiency of both sides of the heart—dyspnea, cyanosis, signs of pulmonary engorgement, swelling of the veins and liver, dependent edema and transudates in the serous cavities, etc It appears that ascites and hydrothorax, like pericardial effusion, in myxedema are not always due to heart failure but may be directly myxedematous (*cf* Marzullo and Franco[25]) The only characteristic feature of the heart failure is that it is relieved by the administration of thyroid and not of digitalis. Where the manifestations of cardiac failure are not alleviated by thyroid therapy, they are not attributable directly to the myxedema but to associated coronary arteriosclerosis or perhaps hypertension, the myxedema, indeed, may militate against the development of cardiac failure through diminishing the work of the heart. Probably most instances of heart failure in elderly myxedematous subjects are of arteriosclerotic origin

Cardiac pain is not rare in the myxedematous Most often it is probably due to coronary arteriosclerosis Long-standing hypothyroidism undoubtedly favors the development of arteriosclerosis Simpson[36] and others have observed severe arteriosclerosis in sheep, goats, and other animals following thyroidectomy. Elderly myxedematous subjects almost always show severe arteriosclerosis; this was present in a man with myxedema who succumbed at the age of twenty-one years It is an interesting point, brought out by Christian,[7] Means, White and Krantz,[28] and others, that the administration of thyroid may elicit anginal attacks in myxedema. This is presumably attributable to the increase in the work of the heart and the consequent elimination of the cardiac rest afforded by the low metabolic rate I have at present under observation a man of forty with classical myxedema in whom cardiac pain has persisted for almost a year while the metabolic rate has been maintained within normal limits by the administration of thyroid extract The pain is not paroxysmal and not precipitated by exertion Fahr has described coronary thrombosis in a woman with myxedema following the administration of thyroid. On the other hand, Ziskin[46]

and Beaumont and Robertson[4] have reported the improvement of anginal pain in myxedema by thyroid therapy, an observation also made by Libman[21] in subjects not obviously myxedematous. In Beaumont and Robertson's patient, either overdosage or underdosage with thyroid was followed by recurrence of anginal pain. The mechanism of the pain and its relief by thyroid treatment in such cases is obscure.

THE BERIBERI HEART

A remarkable cardiovascular disturbance may result from deficiency in vitamin B_1. The existence of this circulatory derangement in the beriberi of the rice-eaters of the Orient has long been known, and has been studied in detail under the name of the "beriberi heart" by Wenckebach and Aalsmeer[43] and Keefer.[20] However, notwithstanding isolated descriptions by Scott and Hermann[35] and others, the occurrence of severe circulatory failure in vitamin B_1 deficiency as it is encountered in the United States was not generally appreciated prior to the important investigations of Weiss and Wilkins.[42]

The large majority of instances of beriberi heart described in northeastern United States have occurred in the avitaminosis of alcoholics. For this reason, apparently, the incidence of the condition varies enormously in different institutions; almost all the cases are observed in municipal hospitals with their numerous alcoholic derelicts Weiss and Wilkins base their report on 120 cases at the Boston City Hospital They encountered cardiovascular disturbances due to vitamin B_1 deficiency in 1 in 160 admissions to the medical wards and state that in their institution it is more common than hyperthyroid heart disease or subacute bacterial endocarditis. At Bellevue Hospital, Jolliffe and Rosenblum[18] found cardiovascular symptoms in 19 of 65 inebriates who presented polyneuritis, Laennec's cirrhosis or other "nutritional complications" of alcoholism. On the other hand, in the past three years since becoming interested in the condition through Weiss's publications, I have recognized no well-defined example of heart failure due to avitaminosis at The Mount Sinai Hospital or in private practice. For this reason, the following paragraphs are based on the above-mentioned publications and a few cases shown me by others.

Heart failure due to vitamin B_1 deficiency is characterized by the curative effect of thiamin and is peculiar in that, like some instances of hyperthyroidism, it occurs in the presence of accelerated peripheral blood flow due to vasodilatation. It appears that the avitaminosis on the one hand impairs functional capacity of the myocardium and on the other exerts some obscure peripheral effect which results in relaxation of the small vessels. The increased venous return due

to the diminished peripheral resistance may in turn augment the insufficiency of the functionally impaired right heart.

The cardiovascular symptoms of vitamin B_1 deficiency are most often associated with polyneuritis, psychosis, cirrhosis, or other consequences of avitaminosis and alcoholism. However, Keefer and others have pointed out that heart failure is most apt to occur in cases of vitamin B_1 want in which the polyneuritis has not been severe enough to curtail much the physical activities of the patient; the rationale is presumably much the same as that of the rarity of heart failure in tabetics with luetic aortic regurgitation. The onset of heart failure may be revealed by weakness, swelling of the feet, exertional or paroxysmal dyspnea, palpitation, cough, or other of the usual manifestations. The objective findings may include edema, distention of the cervical veins, enlargement of the heart, tachycardia, gallop rhythm, manifestations of pulmonary engorgement, enlargement of the liver, and transudates in the serous cavities. Keefer emphasized the necessity for caution in attributing edema in beriberi to heart failure without supporting evidence, for the avitaminosis also produces dropsy through other mechanisms Weiss and Wilkins attribute arteriolar dilatation with resultant increase in capillary pressure a rôle in the production of the edema. Observers in the Orient describe the cardiac insufficiency as most often right ventricular failure, but Weiss and Wilkins also found evidences of left-sided failure Circulatory collapse and sudden death may occur.

Keefer's roentgen studies showed that the enlargement of the heart is predominantly due to dilatation of the right side, though there may also be some dilatation of the left ventricle and auricle At necropsy, dilatation of the right ventricle is generally most striking. Characteristic is the decrease in the size of the heart following the administration of vitamin B_1. The electrocardiogram exhibits abnormalities in most cases, which disappear with the correction of the avitaminosis. The most common in Weiss and Wilkins' patients were changes in the T waves and prolongation of electrical systole (Q–T interval) They also observed extrasystoles and auricular fibrillation, but Wenckebach and Aalsmeer encountered no arrhythmias.

As mentioned above, there are generally evidences of arteriolar dilatation and an accelerated circulation. These may include warm extremities, prominent arterial pulsations, pistol-shot sounds over the arteries, increased pulse pressure, and capillary pulsations. Weiss and Wilkins found that the velocity of blood flow is normal or increased and the arteriovenous oxygen difference decreased even in the presence of elevated venous pressure due to heart failure Inawashiro and Hayasaka[17] found the cardiac output increased.

The mechanisms through which deficiency in vitamin B_1 produce

the peripheral vasodilatation and the heart failure are obscure Wenckebach and Aalsmeer observed the accumulation of droplets of fluid in the heart muscle fibers (hydropic degeneration) and interstitial edema between the fibers. They believe these findings indicate water retention in the heart muscle due to the vitamin deficiency, and that this entails diminution in the contractility of the fibers However, the interpretation of the myocardial changes as due to water retention is opposed by Weiss and Wilkins' finding that the water content of the myocardium of the beriberi heart does not differ from that of controls. Nevertheless, the hypothesis of a metabolic change in the heart muscle due to the avitaminosis seems the most plausible explanation of the cardiac insufficiency.

Pellagra.—Feil[12] observed electrocardiographic changes indicating myocardial damage in 14 of 38 patients with pellagra. Both electrical and mechanical systole were prolonged in some of the patients. Feil points out that acute pellagra is often marked by such subjective symptoms as exertional dyspnea and palpitation, and objectively by tachycardia and feeble heart sounds. However, these cardiovascular manifestations are much less pronounced than in beriberi. Weiss and Wilkins believe the cardiovascular disturbances in pellagra are also due to associated deficiency in vitamin B_1

Orthostatic Hypotension Due to Avitaminosis.—Recently, the writer has encountered an exquisite example of orthostatic hypotension in a woman who had been a "food crank" for many years and had become extremely emaciated. In the erect posture the blood pressure could not be measured and she repeatedly fainted There was peripheral neuritis Large amounts of thiamin and other vitamins were administered with clinical recovery and disappearance of the orthostatic hypotension Presumably, the orthostatic hypotension was due to disturbance in the nervous mechanism regulating the postural adaptation of the blood vessels, such as sometimes occurs in tabes dorsalis.

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CHAPTER XXXI

HYPODIASTOLIC HEART FAILURE

This section is concerned with certain forms of circulatory failure characterized by deficient filling of the heart. So far as is known, subnormal filling of the heart is always due to extracardiac causes and not to intrinsic weakness of the myocardium. Did the heart function as a suction pump, one could conceive of deficient filling due to lessened aspiration by a weakened myocardium. But the evidence available indicates that the heart is at least predominantly, and probably exclusively, a force pump which is filled *passively* when the pressure in the great veins exceeds that within the chambers. Weakness of the heart muscle therefore tends to increase and not to decrease the diastolic filling of the heart. It has not been demonstrated that there exist conditions of "hypertonicity" (page 306) of the myocardium which inhibit diastolic relaxation and consequently the ingress of blood into the heart. Nor is there evidence that hypertrophy of the myocardium interferes with filling.

The mechanisms which lead to deficient filling of the heart belong to two general groups:

1. Disturbances marked by diminution in the volume of circulating blood or increase in the capacity of the small vessels. The result is that less blood enters the great veins in the unit of time, with equal diminution in the venous return to the heart. This is the mechanism of *peripheral circulatory failure* which produces the clinical picture of *shock* and will be considered in Chapter XXXII.

2. Increased resistance to entrance of blood into the heart, either as a result of limitation of the amplitude of diastole with or without compression of the great veins as they enter the heart, or because of abbreviation of diastole in excessive tachycardia. The term *hypodiastolic failure* serves to designate this mechanism, which occurs under three main circumstances:

(*a*) Pericardial effusion.

(*b*) Constrictive pericarditis.

(*c*) Paroxysmal tachycardia.

In the last two conditions, circulatory failure may also be due to myocardial insufficiency (weakness of the pump mechanism, hyposystolic failure), or there may be a combination of insufficient filling with myocardial weakness.

PERICARDIAL EFFUSION

Pericardial effusion furnishes the classical example of circulatory failure due to interference with the diastolic filling of the heart. However, heart failure is so often absent with even large effusions that so keen an observer as Mackenzie[27] stated that the presence of fluid in the pericardial cavity does not seriously embarrass the heart.

Pathological Physiology.—The mechanism of circulatory failure in pericardial effusion was first clearly elucidated by the experiments of Cohnheim.[9] He showed that when oil is introduced into the pericardial cavity under sufficient tension, the entry of blood into the heart is hampered, with the result that it accumulates in the veins and correspondingly less enters the arteries. Cohnheim's studies and the subsequent ones of Starling,[23] Kuno[24] and others have shown that the sequence of events is as follows: As the intrapericardial pressure rises, the venous return meets with increasing resistance, with the result that the pressure in the veins rises and the cardiac output falls Up to a considerable intrapericardial tension, the arterial pressure is unaffected, vasoconstriction apparently compensating for the diminished cardiac output But after a critical level of intrapericardial tension is reached, any further rise is followed by an abrupt drop in arterial tension as the cardiac output falls too low to be compensated by vasoconstriction. As might have been anticipated, Kuno's observations showed that the level of intrapericardial tension required to interfere with the circulation depends on the initial height of the venous pressure, the higher the latter, the more fluid can be introduced into the pericardial cavity before the arterial pressure falls.

How high the intrapericardial pressure may rise as a result of pericardial effusion is shown by a case of tuberculous pericarditis reported by Beck and Cushing,[5] in which the intrapericardial pressure was 21 cm. of water, which fell to zero after the aspiration of only 250 cc of fluid

Significance of the Rapidity of the Effusion.—These experiments show clearly that circulatory failure in pericardial effusion is a function of the intrapericardial pressure rather than of the volume of the effusion This explains the clinical observation that the occurrence of circulatory failure in pericardial effusion is largely dependent on the rapidity with which the fluid accumulates, for the latter is a prime determinant of the intrapericardial pressure that develops. The pericardium is practically inextensible; only a few hundred cubic centimeters of fluid can be introduced into the cavity at one sitting even under high pressure. As a result, intolerable compression of the heart readily occurs when fluid enters the pericardium rapidly. The best examples are seen in hemor-

rhage into the pericardium—as a result of trauma, rupture of an aneurysm, scurvy, or other hemorrhagic diathesis—whereas little as 200 cc of blood have been observed to cause fatal tamponade of the heart. This is the mechanism of the rare instances of sudden death in which comparatively small hemorrhage into the pericardium is found

Relatively rapid effusion into the pericardium also occurs in purulent pericarditis, and then severe circulatory failure may develop within a few hours. In one such case of purulent pericarditis in streptococcal sepsis, the pulse at the wrist was impalpable in less than a day after orthopnea first was noted; removal of 500 cc. of pus by paracentesis was accompanied by restoration of normal blood pressure and disappearance of orthopnea and cyanosis, and yet the necropsy showed that the 500 cc. was almost all the fluid that had been present in the pericardium.

When the fluid accumulates more slowly, as in most instances of rheumatic, tuberculous, or uremic pericarditis, much larger pericardial effusions are usually necessary to produce circulatory failure Indeed, effusions of more than 2 liters have been observed in which there were no indications of obstruction to the circulation, even though there was compression of the left lung and other adjacent structures The reason is that when the fluid accumulates slowly, the pericardium stretches and there is little rise in intrapericardial tension

Structures Compressed by Pericardial Effusion and the Resultant Symptoms.—The parts most susceptible to compression by a pericardial effusion are naturally those in which the pressure is least and the walls thinnest, *i e.*, the great veins and auricles. The sites of compression are determined by the distribution of the effusion Curschmann,[16] Williamson,[40] and others showed that a free pericardial effusion accumulates first along the lower margin of the heart and about the apex, especially along the diaphragmatic surface of the heart. In accord with this, Elias and Feller[13] found that an accumulating pericardial effusion first compresses the inferior vena cava, as well as the mouths of the hepatic veins when, as is often the case, the latter empty into the inferior vena cava partially above the diaphragm The effusion also tends to push the left lobe of the liver downward and, according to Elias and Feller, compress the left hepatic vein where it runs within the substance of the liver close to the diaphragm and parallel to that muscle Elias and Feller found that in such pericardial effusions the compression of the hepatic veins is often more significant than that of the vena cava with its wide lumen, and consequent large factor of safety; the result is that swelling of the liver and perhaps ascites develop before there is edema of the lower extremities However, initial palpability of the liver in pericardial effusion may be due

to downward displacement as well as engorgement; tenderness speaks for the latter. In such cases with hepatic engorgement, the territory of the superior vena cava may be unaffected, as revealed by absence of engorgement in the cervical veins and normal pressure in the antecubital veins

With larger effusions, the auricles, the superior vena cava and the pulmonary veins are also compressed. There is dyspnea, orthopnea, cyanosis, and edema, in addition to the above-mentioned consequences of portal congestion The cervical veins are swollen and the venous pressure in the upper extremities is elevated Often there is strikingly little pulsation in the cervical veins in comparison to their severe engorgement, much less than when the venous stasis is due to right heart failure with its frequent relative tricuspid insufficiency. Likewise, the enlarged liver does not pulsate Evidence of the compression of the superior vena cava may be afforded by swelling of the face, especially in the morning, so that the patient comes to resemble a sufferer from Bright's disease, such swelling of the face hardly occurs in the dropsy of right heart failure Rarely, the compression of the superior vena cava produces swelling of the neck like that of the collar of Stokes in mediastinal tumor. Often, as Elias and Feller point out, there is little evidence of pulmonary stasis, in contrast to the severe engorgement of the territories of the venæ cavæ and the portal vein, basal râles are not audible and the roentgenogram reveals clear lung fields The explanation probably is that the compression of the right auricle, venæ cavæ and hepatic veins allows so little blood to enter the pulmonary circuit that there is no stasis in the lungs despite considerable compression of the pulmonary veins and left auricle. But in other instances, severe pulmonary engorgement develops with agonizing dyspnea and orthopnea, evidently the compression of the left auricle or pulmonary veins is dominant The orthopnea is manifested not only by the patient sitting up but also most often by bending forward, in which position the fluid presumably tends to gravitate against the anterior chest wall and away from the vulnerable auricles and great veins Cases have repeatedly been described in which this position was grotesquely exaggerated so that the sufferer assumed the knee-chest position (*signe de la prière mahométane* of the French), and I have seen one such patient who was promptly relieved by paracentesis. Compression of the left lower lobe and pressure on the left bronchus may also contribute to the dyspnea. The heart sounds are often distant as a result of the fluid and there may be embryocardia On the other hand, gallop rhythm does not result from pericardial effusion. The pulse is rapid and small; rarely, pulsus paradoxus is present The systolic and pulse pressures are usually somewhat decreased. The electrocardiographic changes which are frequently present may include

low voltage of the *Q-R-S* complexes and elevation of the *RS-T* intervals culminating sometimes with improvement in inversion of the *T* waves (*cf.* Oppenheimer and Mann,[29] Master,[28] Barnes[3]). The pathogenesis of the electrocardiographic changes accompanying pericardial effusion are not clear; subepicardial myocarditis and mechanical interference with the coronary circulation as a result of high intrapericardial pressure may be concerned.

When the intrapericardial pressure rises rapidly, notably in hemopericardium and purulent pericarditis, the picture is characteristic and alarming. Orthopnea is severe, cyanosis deep, the hands cold, the cervical veins swollen but scarcely pulsating, and the arterial pressure drops sharply with a small pulse pressure. In extreme instances, the radial pulse may be impalpable. Such findings call for immediate paracentesis.

Long-standing Compression of the Heart by Pericardial Effusion.—Fischer[14] has reported a case in which stab wounds in the cardiac region were followed by heart failure with hydrothorax and ascites. When the man succumbed six months later, the pericardium contained 2100 cc. of old bloody fluid and the heart was very small and evidently shrunken. Fischer termed this state "chronic tamponade of the heart." The condition is evidently very rare, but knowledge of its existence is important, for paracentesis would probably be effective.

CONSTRICTIVE PERICARDITIS

Adhesion of the two surfaces of the pericardium does not necessarily add to the burden of the heart, and is often discovered at necropsy in the absence of cardiac hypertrophy or dilatation in an individual whose circulation was impeccable. Such observations led Laennec[26] and some of his leading contemporaries to the recognition that adhesive pericarditis is often of little clinical significance. But there are also instances in which chronic productive inflammation of the pericardium with or without associated mediastinitis results in severe circulatory failure. Sometimes, recognition that the circulatory failure is due to pericardial and mediastinal induration is difficult, but in other cases the diagnosis is relatively easy. Detection of the condition has become most important in recent years because of the remarkable therapeutic results often attained by surgery.

Chronic productive inflammation of the pericardium and surrounding mediastinum due to tuberculosis or other cause may hamper the circulation in one or more of three ways:

1. **Fixation to the Surrounding Structures.**—The heart may be firmly fixed to the surrounding structures—notably the anterior chest wall, diaphragm, lungs, aorta, and spinal column—by inextensible bands of connective tissue. Normally, when the heart contracts, the space is filled in by expansion of the lungs. The

work required of the heart to draw the lungs with it in systole is negligible. But when the heart is fixed over broad areas to the chest wall, the diaphragm and the spine, the lungs are prevented from filling in the space vacated during systole and traction is exerted on the structures to which the heart is attached. Since the spine is immobile, it serves as a fixed point, and there is systolic retraction of the chest wall and the diaphragm at points determined by the site of the adhesions. Broadbent's sign is due to traction on the diaphragm, which causes a pull on its attachments. The fixation of the diaphragm and the chest wall to the pericardium not only increases the work of the heart directly but also hampers inspiration and decreases the respiratory aid to the venous return to the heart. For the heart to draw with it the above-mentioned structures obviously entails considerable increase in the work performed with each systole. The consequence is hypertrophy and dilatation of the chambers implicated, and when this occurs over a long period in young individuals an enormous heart may be the outcome. Usually, both sides of the heart participate in the hypertrophy and dilatation, but either may be predominantly affected. Of the three mechanical pathogenetic factors in the circulatory failure of mediastino-pericarditis, fixation to the surrounding structures is the only one which leads to an increase in the work of the heart and thus to enlargement of the organ.

Formerly, fixation to the surrounding structures was regarded as the usual mechanism through which adhesive mediastino-pericarditis produces circulatory failure. But the more intensive study promoted by the development of surgical treatment has shown that cases in which this mechanism predominates or is even significant are very rare.

2. Constriction of the Great Veins.—When scar tissue forms as a result of mediastino-pericarditis, either vena cava or the hepatic veins, if their mouths are supradiaphragmatic, may be constricted. Such a process would lead to predominance of venous engorgement in one of the three territories mentioned. But that this mechanism is rarely significant is shown by Burwell's[6] finding, in a considerable number of cases of indurative pericarditis, that the venous pressures in the upper and lower extremities were identical.

3. Incarceration and Constriction of the Heart.—In recent years it has become clear that chronic mediastino-pericarditis interferes with the circulation chiefly, in fact most often solely, through mechanically hampering the diastolic relaxation of the heart as a result of contraction of scar tissue. The process has become generally known as *constrictive pericarditis*, and will be discussed in the following sections.

Effects of Constrictive Pericarditis.—As a result of chronic pericarditis—be it of tuberculous, pneumococcic, or other and usually

obscure etiology*—the two layers of the pericardium may become not only adherent to one another but enormously thickened. Less often, thickening of either or both layers occurs in the absence of widespread adhesion or with fluid between the layers. The thickening is due to the formation of connective tissue, which becomes firm and inextensible and in which extensive calcification may occur. The pericardium has been observed to be as much as 3 cm. thick and of leathery or stony consistence. The scar tissue may exhibit a tendency to condensation and contraction, especially after the active inflammatory process has subsided. The result is that the diastolic relaxation of the heart is mechanically limited, with corresponding diminution in the ability of the heart to increase its output or meet greater arterial resistance. As the pericardium shrinks, the functional capacity of the heart decreases correspondingly until symptoms of circulatory failure appear even at rest. The mechanism of the circulatory failure in incarceration of the heart is beautifully illustrated by the observations of Burwell and Strayhorn.[8] In a patient with *concretio cordis*, they found that the acceleration of the heart during exercise was not accompanied by increase in the stroke volume of the heart above the markedly subnormal value present at rest. Evidently, even under the stimulus of exercise, the thickened pericardium prevented increase in the amplitude of diastole so that the only remaining reserve was acceleration in rate. The heart failure is thus a true *hypodiastolic failure*, due entirely to mechanical limitation in the amplitude of diastole. In accord with this conception of hypodiastolic failure, Beck[4] has found that the muscle fibers in the compressed heart are definitely smaller than normal, quite the opposite of the enlarged muscle fibers which are characteristic of the heart in hyposystolic failure.

Clinical Picture of Constrictive Pericarditis.—The typical clinical picture of constrictive pericarditis is what one would anticipate from a process which mechanically impedes the filling and diastolic relaxation of the heart: *engorgement of the systemic veins and its consequences contrasting with a heart that is not enlarged at all or but slightly so.* An outstanding characteristic of the systemic venous engorgement in a high proportion of the cases, though not all, is the predominance of portal congestion documented by enlargement of the liver and ascites over the other consequences of venous overloading. The clinical picture may simulate Laennec's cirrhosis more than that of the common forms of heart failure. For this reason, Friedel Pick[30] originally described the condition under the

* It is interesting and important, as White has pointed out, that despite the frequency with which rheumatism produces pericarditis, it is rarely, if ever, concerned in the genesis of *constrictive pericarditis*. Tuberculosis was the etiology in 18 of 19 cases studied by Burwell and Blalock,[7] a higher percentage than seems to obtain in New York City. In countries where scurvy often occurs in adults, this is apparently an important cause of pericardial thickening—pericarditis scorbutica

name of "pericarditic pseudocirrhosis of the liver. It is often known as Pick's syndrome, though doubtless there have also been included under this name cases in which the ascites was not a mechanical result of heart failure due to constrictive pericarditis but resulted from true polyserositis with independent tuberculous or other inflammatory disease of the peritoneum.

The initial symptoms may not differ from those of the common forms of heart failure, such as dyspnea on exertion, swelling of the feet, weakness, or cough. But sometimes the patient's attention is drawn to his illness by enlargement of the abdomen due to ascites, which in combination with engorgement of the veins of the neck is immediately suggestive of the diagnosis. A point made by Burwell and Blalock[7] is worthy of emphasis, namely, that the manifestations of systemic venous engorgement in constrictive pericarditis often remain relatively unchanged over long periods of time

The *heart* is normal in size or at most but moderately enlarged In White's[38] 13 cases, the heart was normal in size in 7, slightly enlarged in 5, and moderately enlarged in 3 In the cases in which the teleoroentgenogram reveals slight or moderate enlargement of the cardiac silhouette, the heart itself may not be enlarged at all, the augmented dimensions being due to enormous thickening of the pericardium Fluoroscopy most often, though not invariably, reveals definite diminution in the amplitude of the ventricular excursions, this is the more significant the smaller the heart. The diagnosis may be aided by the demonstration of diminished pulsations in the roentgen kymogram (*cf* Gubner *et al* [17]). The roentgenray examination sometimes discloses pericardial calcification One may find that the heart is displaced little by change in position, this is also the more significant the smaller the heart, but I have rarely found the maneuver of definite aid in the diagnosis Most often the heart rate is accelerated The rhythm is usually regular, exceptionally, the auricles fibrillate As would be anticipated with an imprisoned heart, neither the apex beat nor other impulses are prominent Contrary to the hyposystolic forms of heart failure, gallop rhythm does not appear. Indeed, there are no auscultatory signs referable to the pericardial constriction The electrocardiogram generally shows low voltage of the *Q-R-S* complexes and *T* waves in the limb leads, and there may be cove plane inversion of the *T* waves (Sprague,[32] Cushing and Feil[12]). Increase in voltage has been observed following successful operation Fixation of the electrical axis in different positions of the body has been described as an electrocardiographic sign of mediastino-pericarditis. However, it is at best equivocal evidence, Simpson and Rosenblum[31] and France[16] have shown that there may be considerable shift of the electrical axis in patients with constrictive pericarditis and that, on

edema is likewise variable. In some instances, there is marked *edema* of typically cardiac distribution. But what is of especial importance is that in the Pick syndrome with recurrent ascites and enlargement of the liver, edema of the lower extremities may be entirely absent or minimal. In some of the cases, puffiness of the face, especially in the morning and simulating the edema of Bright's disease, may occur, it is presumably due to implication of the superior vena cava in the mediastino-pericarditis. Pleural transudates are common.

Ascites and Enlargement of the Liver.—In most instances copious and recurrent ascites dominates the clinical scene. Only rarely, if ever, is abdominal transudation absent throughout. Not uncommonly, in contrast to other forms of heart failure, the ascites exists in the absence of edema of the lower extremities. The initial complaint is often due directly to the peritoneal effusion; the patient suffers from abdominal distention or oppression, and notices that his abdomen is increasing in size. The ascites recurs, sometimes over a period of many years; 1 patient was tapped 301 times, and I saw a case in which a total of some 350 liters were removed. In cases passing as "cirrhosis of the liver" in which repeated tapping has been carried out for a period of over a year, one does well to search carefully for evidences of constrictive pericarditis.

The liver is palpably enlarged, and may be very massive and firm; the edge may be either sharp or rounded. The spleen may also be palpable and firm Examination of the abdominal viscera at postmortem may reveal a characteristic picture. The peritoneum, especially in the upper abdomen, is usually thickened to a varying degree. The peritoneal thickening is often best marked over the liver so that the organ is enclosed in a thick, tough connective-tissue sheath—the iced liver (*Zuckergussleber*) of Curschmann[11] The liver is generally enlarged and firm. In some cases of long duration the liver shrinks to almost a normal, or rarely even a subnormal, size. The cut section may or may not present the nutmeg appearance of chronic passive congestion. In some cases there is considerable "cardiac cirrhosis" (page 252), but in others there is surprisingly little connective tissue within the organ despite the fact that ascites has recurred for years The spleen is generally enlarged and there may be perisplenitis similar to the change in the capsule of the liver

The ascites and enlargement of the liver are doubtless due to the systemic venous engorgement resulting from the constrictive pericarditis This conception was maintained by Pick in his original communication, but later some clinicians regarded the thickening of the peritoneum and ascites as manifestations of independent inflammation of the peritoneum (*cf.* Kelly[23] for the older literature). However, the production of the ascites by the mechanical obstruc-

tion of the thickened pericardium would appear to have been proved beyond cavil by the disappearance of the peritoneal effusion following successful surgical removal of the pericardial impediment Moreover, Flesch and Schlossberger[15] and Beck[3] have produced obliteration and thickening of the pericardium by the injection of irritating substances into the pericardial cavity of animals, with a resultant picture simulating the Pick syndrome, including ascites The thickening of the capsule of the liver and other parts of the peritoneum which older investigators considered as evidence of independent chronic peritonitis may well be, as indicated by Pick and maintained by Volhard,[36] a *consequence* of engorgement and ascites of very long duration, moreover, it is not present in all cases It should also be remembered, in this connection, that when a transudate has been present for a long time, it tends to assume the high specific gravity and other attributes of an exudate.

The foregoing description is concerned with *constrictive* pericarditis, in which the ascites is a *mechanical* consequence of the pericardial disease. There are also cases, though they appear to be very rare in New York City, in which adhesive pericarditis and peritoneal effusion are parts of a *polyserositis* (sometimes called Concato's disease), the ascites being of inflammatory origin and not a mechanical consequence of mediastino-pericarditis Such a state of affairs obtains in some tuberculous patients, especially in children, where tubercles of various ages are found on the peritoneum In some of these instances of association of tuberculous pericarditis with ascites, Hutinel[20] and other French clinicians have found tuberculous cirrhosis of the liver (*cirrhose cardio-tuberculeuse*), this is apparently rare and I have not encountered it Cases of polyserositis of other than tuberculous, and as yet obscure, etiology also occur, but are very rare

How constrictive pericarditis produces enlargement of the liver and ascites in the absence of notable edema of the lower extremities is a puzzling question It is not through the intermediacy of periportal cirrhotic changes in the liver, for these are not marked and may be entirely absent. In a number of instances, compression or kinking of the intrapericardial portion of the inferior vena cava by the pericardial scar has been observed, but it is not evident why this should cause isolated engorgement of the liver and portal territory. Implication of the mouths of the hepatic veins, when they empty into the vena cava above the diaphragm (Hasse[18]), would offer a plausible explanation, but, while some suggestive observations are cited by Elias and Feller,[13] actual evidence is lacking Wenckebach[37] believes that diminished mobility of the right half of the diaphragm, due to mediastinal and pleural adhesions, inhibits the inspiratory "squeezing out" of the liver and thus predisposes to portal engorgement; but this is merely a hypothesis

It seems evident that the actual mechanism through which mediastino-pericarditis causes recurrent ascites in the absence of edema of the lower extremities is as yet obscure.

DEFICIENT FILLING OF THE HEART DUE TO TACHYCARDIA

Acceleration of the heart rate may so shorten diastole as to allow insufficient time for the filling of the ventricles, with resultant circulatory failure The relations between the rate and the output of the heart have been discussed on page 294. There it is pointed out that the output of the heart increases *pari passu* with the rate up to a limiting rate determined by various factors, beyond which further acceleration results in decrease in cardiac output.

Ventricular rates which abbreviate diastole enough to diminish diastolic filling significantly may occur in paroxysmal tachycardia, auricular flutter, and auricular fibrillation. However, in auricular fibrillation and flutter, the rapid rate of the auricles is most often accompanied by sufficient depression in auriculo-ventricular conduction to reduce the ventricular rate to one at which it is not probable that the length of diastole is inadequate for ventricular filling. Moreover, continuous auricular fibrillation most often occurs in patients with myocardial insufficiency and elevated venous pressure, so that filling is accelerated. It is in paroxysmal tachycardia and auricular flutter that one is more likely to encounter abbreviation of diastole sufficient to interfere seriously with ventricular filling.

Heart Failure in Paroxysmal Tachycardia.—In paroxysmal tachycardia, the ventricular rate rises abruptly to between 120 and 220 per minute, sometimes even more. The rapid cardiac action lasts from a few moments to days, rarely weeks. In the vast majority of such attacks, even with rates above 200, there are no signs of circulatory failure, and the patient's symptoms are those due directly to the rapid heart action, such as fluttering in the chest or neck, or a vague sense of uneasiness, perhaps due to consciousness of the heart's action. But in exceptional instances, evidences of circulatory failure develop These are of two types.

1. Symptoms of Inadequate Blood Flow Due to Decrease in the Output of the Left Ventricle.—How marked such decrease may be was shown by the measurements of Barcroft, Bock and Roughton[1] which revealed that during an attack of paroxysmal tachycardia the cardiac output fell to about 33 per cent of the previous value. The most important symptoms of arterial ischemia are those due to diminution in the blood flow to the brain. Most often, these consist merely in giddiness or faintness that is promptly relieved by reclining. Rarely, loss of consciousness, various focal cerebral phenomena, convulsions, or Cheyne-Stokes breathing develop. The

pallor of the skin that is so often present is probably due to peripheral vasoconstriction induced by the diminished output of the heart and tending both to maintain the arterial pressure and to divert a larger fraction of the small cardiac output to the vital organs Despite this probable vasoconstriction, the arterial pressure often falls moderately, rarely even considerably.* The pulse pressure falls more than the systolic pressure, because the diastolic tension is depressed but little or not at all, and may actually rise. One factor which militates against fall in diastolic pressure is the shortening of diastole, which allows less time for the arteries to empty, and another element may be the compensatory vasoconstriction mentioned above. As a result of the minute stroke volume due to the rapid ventricular rate and the small pulse pressure, the radial pulse may be nearly impalpable or merely a slight undulation despite a systolic arterial pressure of 90 mm. of mercury or more and tolerable well-being of the patient.

2. Consequences of Venous Engorgement.—When venous engorgement develops, it is almost always confined to the systemic veins; as emphasized by Wenckebach,[37] severe pulmonary congestion is a rarity. Apparently, the diminution in filling of the right ventricle results in so little blood entering the lesser circulation that the left ventricle can master it despite the short diastole. Nevertheless, there are rare instances, as one cited by Wenckebach, in which the left side of the heart constitutes a *locus minoris resistentiæ* in consequence of mitral stenosis, hypertension or other previous disease, so that an attack of paroxysmal tachycardia results in pulmonary engorgement or even edema of the lungs. The most common manifestations of venous engorgement in paroxysmal tachycardia are swelling of the systemic veins and liver with rise in venous pressure. These usually develop only after the attack has lasted for several days. However, especially if there has been previous motor weakness of the heart, the liver may descend almost to the level of the umbilicus within a few hours and become very tender. Cyanosis of the lips and finger tips may contrast with the general pallor of the skin. Dyspnea is rarely marked, presumably because of the infrequency of pulmonary engorgement.

Two signs which under other circumstances are indicative of grave circulatory failure do not have this significance with the rapid heart rates of paroxysmal tachycardia, namely, embryocardia and pulsus alternans. They are merely manifestations of the rapid heart rate Nor do occasional large waves in the veins of the neck express heart failure; as pointed out by Wenckebach, they result

* However, in some episodes of paroxysmal tachycardia, the blood pressure rises during the attack I have observed this in two attacks in one patient Whether the elevation in arterial tension was due to increased cardiac output or to vasoconstriction was not evident

from overlapping of auricular and ventricular systoles due to the shortness of diastole.

Pathogenesis of Heart Failure in Paroxysmal Tachycardia.—Two factors may be concerned in the production of heart failure in paroxysmal tachycardia, namely, insufficient filling of the heart due to the shortness of diastole, and fatigue of the myocardium. An indication of which of these factors predominates in a given case is afforded by the size of the heart, for insufficient filling tends to decrease the volume of the heart and myocardial fatigue to enlarge it. Further comparative studies of the size of the heart during and after episodes of heart failure in paroxysmal tachycardia are needed to determine the relative significance of the two pathogenetic factors

It was long ago observed (Hoffmann[19]) that the heart often does not enlarge even in prolonged attacks of paroxysmal tachycardia, and more recent roentgenographic observation (Vaquez and Bordet[35] and others) have shown that it may diminish in size. Absence of cardiac enlargement while heart failure exists has been observed, revealing the significance of decreased filling in the causation of the cardiac insufficiency. Moreover, in these cases in which the symptoms of circulatory failure develop soon after the onset of the abnormal rhythm, and in which the heart is functionally competent between the attacks, it would appear probable, *a priori*, that insufficient filling of the heart is the sole or predominant pathogenetic factor.

In other episodes of paroxysmal tachycardia, the appearance of symptoms of heart failure is accompanied by demonstrable enlargement of the heart, which rapidly recedes after the attack is over. This is most often the case when heart failure first appears after the attack has lasted several days However, Kahlstorf[21] observed enlargement of the heart as early as two hours after the onset of a paroxysm of auricular flutter Dilatation of the heart is more apt to result during paroxysmal tachycardia in individuals who have manifest structural disease of the heart, but may also occur in those in whom a cardiac lesion is not evident The development of cardiac dilatation reveals myocardial fatigue. Considering the marked abbreviation of the rest period of the heart in paroxysmal tachycardia, and the increased oxygen consumption of the heart muscle at rapid rates (page 295), it is surprising that myocardial fatigue and consequent dilatation are not more common during the attacks. Perhaps the explanation lies partially in the lessened work that the heart is called upon to perform because of the diminished filling. Death from circulatory failure during an attack of paroxysmal tachycardia is very rare; I have not witnessed it. According to Hoffmann, fatal circulatory failure probably occurs only in the presence of manifest disease of the heart muscle.

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CHAPTER XXXII

PERIPHERAL CIRCULATORY FAILURE AND SHOCK

EVERY physician is only too well acquainted with a symptom complex which has been known since the beginning of the nineteenth century as shock.* It is characterized by weakness, pallor, profuse perspiration, feeble or impalpable pulse, and cold extremities The symptom complex occurs under a great variety of circumstances. following trauma, operation or hemorrhage, complicating the infectious fevers, as a prompt sequel of rupture of an abdominal or thoracic viscus, at the onset of myocardial infarction due to coronary thrombosis, in pulmonary embolism, as the result of intractable vomiting or diarrhea, in acute pancreatitis, after extensive burns, in heat stroke, as a manifestation of anaphylaxis, in diabetic acidosis, in the crises of Addison's disease, and in many other conditions Whatever the illness, the terminal picture is most often that of shock. Formerly, the word shock was largely confined to the above-mentioned symptom complex when it occurred after trauma or operation—so-called surgical shock. That the same symptom complex occurs under many other circumstances has only recently been appreciated, and Atchley[1] has spoken of "medical shock."

Needless to say, the clinical manifestations of shock are not identical in all these variegated conditions Nevertheless, whatever the circumstances in which shock develops, certain fundamental features are always present which testify to the existence of a basically identical disturbance in the dynamics of the circulation. It will be seen below that *this disturbance in circulatory dynamics common to all varieties of shock is a diminution in cardiac output which results in inadequate blood flow to at least a large part of the body.*

To repeat, shock is a purely clinical concept born at the bedside, which arose from the need of the practitioner to designate an aggregation of symptoms—weakness, pallor, cold extremities, profuse sweating, and feeble pulse—which he encounters as the dreaded result of various diseases Long after the clinical conception of shock had become a part of bedside thinking, investigation established that the symptom complex results from inadequate cardiac output. The connection between the deficient cardiac output and the symptoms of shock is twofold:

* According to Groeningen,[88] in whose monograph copious historical data are available, James Lata, in 1795, was the first to use the word shock in its current medical connotation

1. The primary cause of the symptoms is the decreased blood flow to the various organs which is an immediate result of the lessened cardiac output.

2. The decreased cardiac output calls forth (probably reflexly) a vasoconstriction which is most marked in the extremities, the skin, and perhaps the kidneys. This selective vasoconstriction produces a redistribution of blood with a larger fraction of the small cardiac output going to the heart, brain and other immediately vital parts of the body. This redistribution of blood favors the survival of the organism, but it results in relatively greater ischemia of the extremities, skin and certain other parts than would be the case if the selective vasoconstriction did not occur

Shock is thus the state which results when the volume of circulation becomes grossly inadequate for the needs of the body Mechanisms are then brought into play which produce vasoconstriction in the limbs, skin and various glandular organs (page 631), and thus divert almost all the small cardiac output to the most immediately vital organs of the body. Figuratively speaking, *shock is a retreat of the circulation; the organism abandons its outposts in the extremities to protect its capital in the central nervous system, heart, and other immediately vital organs.*

On the basis of the origin of the decrease in cardiac output, two main varieties of shock are to be differentiated:

1. Shock due to heart failure of acute origin or intensification—*cardiac shock.* The outstanding examples are seen in the acute left heart failure of coronary thrombosis and the acute right heart failure of pulmonary embolism.

2. Shock due to disturbances originating in the periphery of the circulation—*peripheral shock*, or shock due to peripheral circulatory failure.

Peripheral Circulatory Failure.—The distribution of the cardiac output to the various organs and the return of blood to the right auricle are effected through numerous and complicated mechanisms. As could be anticipated, these mechanisms may be disturbed in a variety of ways, with the result that the blood which is pumped by the heart is not adequately returned to this organ. Since, so far as is known, the heart functions only as a force pump and not as a suction pump, it cannot compensate for defects in the peripheral mechanisms which entail a deficient venous return, and the result is an equal decrement in the cardiac output. The term peripheral circulatory failure serves as a generic designation for circulatory failure originating in this fashion. There are many forms of peripheral circulatory failure; they differ in many respects but have in common the defining characteristic of deficient venous return to the heart. The latter in turn entails an equal decrement in cardiac output, and it is the symptoms resulting from the diminished volume

of circulation that dominate the clinical picture and are collectively known as shock.

Peripheral circulatory failure with resultant shock occurs under numerous circumstances; it is doubtless of far more frequent occurrence than heart failure. Indeed, Henderson[60] pointed out that peripheral circulatory failure is the usual mechanism which ushers in death, whatever the underlying cause. But varied as are the circumstances which produce the sequence of peripheral circulatory failure, diminished venous return, decreased cardiac output, and the clinical picture known as shock or collapse, they fall naturally and usefully into two great categories:

1. *Oligemic*, in which the inadequate venous return is due to diminution in circulating blood volume.
2. *Motor*, in which the inadequate venous return to the heart is due to alterations in the state of contraction of the vessels whose synergistic function is essential to the maintenance of the venous return It is possible that in some of these conditions, a secondary element of oligemia enters as a result of increased permeability of relaxed capillaries

The fundamental feature of the distinction is that in the one instance the circulatory failure is due primarily to an alteration in the blood, in the other to a change in the vessels.

Oligemic peripheral circulatory failure occurs under a great variety of circumstances The causative decrease in circulating blood volume may be due to extravasation of whole blood or to diminution in the volume of circulating plasma alone. Peripheral circulatory failure produced by loss of whole blood is seen in hemorrhage. Recent investigations have shown that peripheral circulatory failure and shock due to diminution in circulating plasma volume occur under a wide variety of circumstances, *e. g.*, secondary traumatic, surgical shock, diabetic coma, Addison's disease, intestinal obstruction or vomiting of other causation, and other varieties of dehydration.

In the *motor form of peripheral circulatory failure* the diminished venous return is due to alterations in the state of contraction of the vessels, or to deficiencies in the extravascular aids to venous return, so that the blood is not propelled back to the heart in adequate quantity. Most often, it appears, relaxation of certain of the small vessels so greatly increases their potentially enormous capacity that the surplus which returns to the heart is inadequate. The circumstances in which this occurs are not as well known as are those of oligemic shock, because there is no single numerical criterion for defining them, as is true of measurement of the circulating blood volume in oligemic shock. However, the almost instantaneous occurrence of the peripheral circulatory failure in so-called primary traumatic shock or following the perforation of a viscus indicates

that the cause of the deficient return must lie in the motor mechanism, since time is lacking for extravasation of sufficient blood. The circulatory collapse which constitutes a danger in spinal anesthesia is also of the motor type It remains to be demonstrated to what extent peripheral circulatory failure in the infectious fevers is due to oligemia and how far it results from motor insufficiency of the small vessels.

What is here designated as the motor type of peripheral circulatory failure was formerly considered as practically always due to relaxation of the arterioles However, it appears that the arterioles have been too universally incriminated in this regard Recently, Smith[103] and his associates (*cf* page 652) have shown that in the circulatory collapse of spinal anesthesia the primary pathogenetic factor is relaxation of the postarteriolar vessels with resultant stagnation of blood in their capacious bed Likewise, Weiss[120] and his collaborators have found that when circulatory collapse is *induced by the administration of sodium nitrite in the erect posture,* the deficient venous return and resulting circulatory failure are also due to stagnation of blood downstream to the arterioles. Indeed, there is good evidence that the relaxation of venules is at least sometimes accompanied by arteriolar constriction. Doubtless, as time goes on, the motor form of peripheral circulatory failure will be further subdivided into varieties due to relaxation of the arterioles, capillaries, and venules Perhaps, also, as maintained by Henderson, loss of tone of the skeletal muscles will be revealed as a significant cause of peripheral circulatory failure (page 629) It appears further that the circulatory collapse underlying anaphylactic shock in some animals is due to spasm of the hepatic or other large veins with consequent trapping of blood behind the obstruction (page 66), whether analogous forms of circulatory failure occur in man remains to be determined.

In the following we shall first describe the general clinical picture of shock as it is seen in peripheral circulatory failure Then the peculiarities of the individual forms of shock will be described in conjunction with a discussion of the pathogenesis of the underlying circulatory failure in the particular condition. This will be done in the following order:

I. Peripheral circulatory failure and shock due to oligemia
II. Peripheral circulatory failure and shock due to motor dysfunction of the vessels
III. Cardiac shock.
IV. Peripheral circulatory failure and shock in acute febrile infections These conditions are considered separately because little is known concerning the pathogenesis of the peripheral circulatory failure Moreover, the myocardium is often damaged by the infection so that there is combined peripheral and cardiac failure.

THE CLINICAL PICTURE RESULTING FROM PERIPHERAL CIRCULATORY FAILURE (SHOCK)

The patient in full-blown shock lies flat in bed; often, he is more comfortable without a pillow. The face is pale and the cheeks are hollow. The lids are frequently almost closed and the eyeballs appear sunken in their sockets. The state of consciousness varies greatly. Syncope may usher in shock. Many patients in severe shock quickly lapse into an apathetic state, indifferent to their surroundings and responding but slowly and feebly to questions or other stimuli. On the other hand, there are also numerous cases in which the victim is alert and consciousness is retained until close to the end Such patients may be pulseless and yet understand everything that is said to them and reply sensibly, if slowly, to any questions asked. The voice is often husky or hoarse. Thirst is a common and often increasing complaint, but the patient frequently vomits what he drinks. Often, though readily roused, the sufferer lies for hours or even days with a vacant expression in his eyes, seemingly entirely oblivious to his environment. Sensation may be so dulled that the patient does not complain of a frightful wound, the pain of coronary thrombosis, or some other lesion that ordinarily evokes agony, and may do so after he has come out of shock. In other instances of shock, the erethic form of the older clinicians, the patient is excited and restless, crying out and tossing about from one side of the bed to the other; he may become incoherent or even maniacal. A common sequence of events is for the patient to be first restless and then become more and more torpid, either spontaneously or under the influence of morphine. While most individuals in severe shock are extremely weak, though nowhere paralyzed, and can hardly raise their hand, it is sometimes astounding how strong a practically pulseless patient proves to be when the effort is made to restrain him. In fatal cases, the duration of the final coma varies from a matter of minutes to even days in a pulseless state.

The *skin* is pale, even cadaveric. The lips usually appear bloodless, but in other cases they, as well as the tip of the nose and nail beds, are cyanotic; most often, such cyanosis is grayish. The grayish cyanosis may be widespread over the surface of the body. Drops of sweat can often be seen on the face and in the axillæ and the perspiration may drench the bedclothes. In severe shock, the general pallor of the skin is often variegated by bluish-red mottling, the so-called *cutis marmorata*. This may be widely diffused, notably in acute pancreatitis, or confined to the abdomen or another part. The mottling is the expression of irregular filling of the superficial capillaries and subpapillary venous plexuses, areas of dilatation and engorgement alternating with others in

which the minute vessels are contracted or empty. The skin feels cold and clammy, especially at the distal points of the circulation in the hands, feet and nose. The turgor of the skin is often diminished in severe shock so that pinched-up folds persist. The low temperature of the skin is especially pronounced when compared with the rectal temperature; a patient in shock with rectal temperature of over 102° F. may have a cool skin and cold hands and feet. On the other hand, if a hot-water bag be applied to a cold part, it warms more rapidly and to a greater degree than in health; this observation testifies eloquently to the severe impairment of the temperature-regulating function of the skin that results from peripheral circulatory failure.

Respiration is usually superficial and accelerated, often interspersed with sighing. However, especially preterminally or under the influence of morphine, the breathing may be slow and so superficial as to be hardly visible. Feeble breath sounds and small moist râles often appear at the bases early in shock. Their origin is obscure; they may bespeak atelectasis due to decreased pulmonary blood flow. If such is the case, the bronchopneumonia which so often appears is due to secondary infection of atelectatic lung.

The *pulse* is usually rapid, but may slow greatly in the terminal phases. What is most characteristic, however, is the low tension, down to impalpability. Even in a fully conscious patient, one may not be able to feel the beat of any of the superficial arteries.

The *blood pressure* is almost always depressed and may be so low that no reading can be obtained by either the palpatory or the auscultatory methods. Both the systolic and the diastolic values are affected, more or less proportionately; with very low systolic pressure, it is often impossible to obtain even a rough estimate of the diastolic tension. In a general way, the height of the blood pressure parallels the general condition of the patient. However, there are instances of otherwise characteristic shock—with pallid, sweating skin, cold extremities, and low venous pressure—in which the arterial tension is maintained for hours or even days at the normal level, or even higher in patients with pre-existent hypertension. The fact that I have encountered such anomalous behavior of the blood pressure especially in coronary thrombosis is perhaps because I have followed this condition more carefully than other states of shock; the same phenomenon was occasionally noted in wound shock during the World War. The significance of the exceptional maintenance of arterial tension in peripheral circulatory failure is discussed below. Observations were made during the World War indicating that the arterial pressure may rise above the normal before the fall which is so characteristic of

shock; this is apparently a consequence of arteriolar constriction in the extremities and perhaps elsewhere (page 631).

The acceleration of the *heart* rate has already been mentioned; often, the rate exceeds 140 beats per minute. In so complex a disturbance, it is difficult to trace the pathogenesis of the tachycardia. It may be due to a reflex initiated by the low blood pressure in the aorta and carotid sinuses. On the other hand, the low pressure in the veins and auricles would tend to slow the heart through the mechanism of the Bainbridge reflex (page 295). There are actually unusual cases in which the heart beat is not quickened and it often slows terminally, presumably as a result of anoxia of the pacemaker. During the tachycardia, the *diastolic pause* is abbreviated and the first sound loses its muscular quality so that it becomes almost identical with the second sound. The result is embryocardia, of which perhaps the most exquisite examples are heard in shock. The sounds may be scarcely audible. Especially in coronary thrombosis, but also in other forms of shock, gallop rhythm may be present and probably indicates that the peripheral circulatory failure has been complicated by myocardial weakness, perhaps as a result of deficient coronary flow due to the low arterial pressure. In accord with this conception, I have observed at necropsy of individuals who succumbed to peripheral circulatory failure (surgical shock, vomiting) disseminated foci of myocardial necrosis sufficiently large to be detected macroscopically; the coronary arteries were not stenosed in these cases. The heart is not enlarged in pure shock. On the contrary, there is every reason to believe that characteristically the heart diminishes in size as a result of the deficient filling due to the small venous return. I have had a few opportunities to see bedside films of patients in shock which seemed to indicate small hearts, but of course such films are difficult to interpret because of the short distance from the chest at which they are taken and in the absence of subsequent films taken with the same technic for comparison. Systematic radiographic studies on this theoretically interesting point would be highly desirable, but are difficult to carry out because of the precarious condition of the patients. In shock produced experimentally in animals, the heart is diminished in size. I have repeatedly seen electrocardiographic changes bespeaking myocardial damage in patients with peripheral circulatory failure, they presumably correspond to the abovementioned ischemic lesions of the myocardium due to diminished coronary flow.

The superficial *veins* are collapsed. This is often painfully evident when one attempts to put a needle in a vein. The veins are very slow in filling when the hand is lowered below the level of the heart or when a tourniquet is applied, and may not even then

become visible: The venous pressure is low and often amounts to only 1 or 2 cm. of water. In severe shock, the blood may not rise at all in a manometer connected to a needle in an antecubital vein This depleted state of the veins is perhaps the most characteristic feature of the clinical picture of peripheral circulatory failure, it should be carefully studied in every case, even though no apparatus for measuring venous pressure is available, by observing the poor filling of the superficial veins of the upper extremity when the hand is held below the level of the heart

The *pupils* are generally dilated in severe shock and react sluggishly, if at all, to light Where there has been considerable dehydration, the eyeballs are soft and sunken The tendon and superficial reflexes are diminished or abolished While there is usually marked muscular asthenia and swallowing may be difficult, paralyses are not evident In the shock of coronary thrombosis, Friedfeld and the writer[42] found that the tension of the *cerebrospinal fluid* is very low.

The *urinary volume* is diminished and the patient may become completely anuric, catheterization yielding no urine. Such urine as is passed is usually free of albumin unless some other cause for albuminuria is present The specific gravity of the urine is most often high and may exceed 1 030 But in other cases the concentration of the urine is not as high as would be anticipated from the small urinary volume. I have repeatedly observed low specific gravity of the urine—sometimes fixed at about 1 010 or 1 012 for days at a time—despite a twenty-four-hour urinary volume of only about 300 cc. and marked elevation of the non-protein nitrogen content of the blood Such coincidence of small urinary volume and low specific gravity of the urine is unequivocal evidence of impairment of renal function Presumably, the impairment of renal function is due to a cutting down of blood flow through the kidney, which results not only from the diminution in cardiac output but also from the arteriolar constriction in the peripheral organs that has been demonstrated in shock and doubtless includes the kidneys (page 631). The impairment of the concentrating ability of the kidney due to diminished blood flow in shock is presumably analogous to the hyposthenuria that occurs in some instances of severe and protracted anemia Physiological experiments show that the oxygen consumption of the kidney is very high, and it seems plausible that when the supply of oxygen is limited because of decrease in blood flow or in the oxygen-carrying capacity of the blood, the ability to form a concentrated urine will suffer.

With marked oliguria and low concentration of the urine, and especially with anuria, there is *retention of urea* and other non-

protein nitrogenous constituents in the blood. Exceptionally, the non-protein nitrogen of the blood exceeds 100 mg. per cent and rarely 200 mg. per cent. Very high azotemia is usually encountered in those cases in which the urinary output is cut down not only as a result of the circulatory disturbance *per se*, but also by severe vomiting or diarrhea. In such patients, the chloride, fixed base and total electrolyte content of the blood may be markedly depressed by the extrarenal loss of salts (page 643). Doubtless, increased destruction of protein favors the azotemia in cases with high fever or extensive tissue necrosis.

Acidosis, revealed by decrease in the carbon dioxide combining power of the blood, is common in shock of any considerable duration. In wound shock, Cannon[21] found a rough parallelism between the alkali reserve and the blood pressure. The carbon dioxide combining power of the blood may fall as low as 20 volumes per cent, but this is usually preterminal. The acidosis is probably of complex causation Since it almost always develops in severely oliguric patients, renal retention is concerned. The decreased blood flow through the muscles, liver, and other organs also plays a part The resultant diminished oxygen delivery has the consequence that lactic acid and perhaps other intermediary products of metabolism are not oxidized as completely as in health. MacLeod[77] found that the lactic acid content of the blood is increased in severe experimental shock. Further, the patients are often unable to ingest or retain food and starvation acidosis due to ketosis may be added; occasionally, ketone bodies are present in the urine. In some forms of shock, the fixed base of the blood is depressed, this being the *cause* of the circulatory failure (page 643). Henderson and Haggard[61] considered the fall in blood alkali as compensatory to depression of the carbon dioxide content of the blood resulting from hyperventilation, but in at least most instances of human shock this factor does not seem significant. In those varieties of peripheral circulatory failure which complicate high intestinal obstruction or other conditions with severe vomiting, the loss of chloride may overcome the other factors and result in *alkalosis*.

Moderate *hyperglycemia* is often present in shock; it is perhaps a manifestation of hypersecretion of epinephrin which is part of the mechanism for constricting the arterioles (page 628).

The most constant effect of peripheral circulatory failure on the *temperature* is, as already mentioned, that the skin is much colder in relation to the rectal temperature than in health. Peripheral circulatory failure affects the internal temperature in several ways. The diminished volume of blood flow lessens the oxygen available for oxidations. It is true that oxygen utilization is not diminished

as much as is the volume of blood flow, for a higher proportion of such oxygen as does circulate is removed on each passage through the capillaries. Aub and Cunningham[6] found in experimental shock that the oxygen content of the venous blood is greatly lowered and the arteriovenous oxygen difference increased. The decreased venous oxygen saturation is often very obvious in human peripheral circulatory failure from the color of the blood obtained on venepuncture. Since, in the absence of pulmonary lesions, there is no reason to assume arterial anoxemia, the low oxygen saturation of the venous blood indicates a high arteriovenous oxygen difference. But this increase in the arteriovenous oxygen difference does not fully compensate for the decrease in volume of blood flow; Henderson, Prince and Haggard,[62] as well as Aub,[5] found that the *basal metabolism* (oxygen consumption) is markedly lowered in severe experimental shock. Such depression in oxidation is, of course, accompanied by corresponding decrease in heat production and must tend to lower body temperature. The same is true of the increased evaporation due to the profuse perspiration of most patients with peripheral circulatory failure. In some instances, hyperventilation may increase heat loss. Exposure to cold after injury is sometimes a potent factor in lowering the body temperature. On the other hand, the diminished blood flow through the skin revealed by the intense pallor must interfere with heat loss and tend to keep up the temperature. The resultant of these factors varies in different types of peripheral circulatory failure. In wound shock during the World War, where the victims were often out in the cold for considerable periods, the rectal temperature was characteristically low, instances of well below 95° F. were observed. Hypothermia is also not rare in other forms of severe shock. On the other hand, if the primary disease is febrile, high rectal temperature may be maintained despite severe peripheral circulatory failure. In myocardial infarction, the temperature may be high notwithstanding severe shock Such fever often develops in the absence of bronchopneumonia and has been attributed to the necrosis of the heart muscle. I have been impressed—a point to which Levine[71] called attention—by the great difference between the cold skin and high rectal temperature in a number of instances of shock due to coronary thrombosis or intestinal obstruction, and it seems plausible that the inhibition of the temperature-regulating function of the skin due to diminished blood flow plays a significant part at least in accentuating elevation of the internal temperature.

The *volume and concentration of the blood* will be considered further on in conjunction with the pathogenesis of the individual forms of peripheral circulatory failure

I. PERIPHERAL CIRCULATORY FAILURE AND SHOCK DUE TO OLIGEMIA

An enormous advance in the understanding of shock has been the demonstration that most of the common forms result from a diminution in the circulating blood volume. The problem of the pathogenesis of these forms of shock has thus been largely reduced to that of the mechanism of the oligemia. Realization of the importance of oligemia in the pathogenesis of peripheral circulatory failure and consequent shock was first attained as a result of investigations during the first World War on the nature of the shock which so often followed wounds. Most of what is known concerning the nature of shock in general is an outcome of these studies of traumatic shock, which will therefore be considered first.

TRAUMATIC SHOCK

Traumatic shock* presents the paradigm of peripheral circulatory failure. Following an injury, the clinical picture of shock just described is seen in its least adulterated form, complicated only by the local manifestations of the trauma. The latter, however, may be displaced far into the background by the gravity of the circulatory failure. Often, the wise physician devotes his attention almost entirely to the latter, considering the wound, for the moment, solely from the point of view of its relation to the general condition of the patient.

Shock may develop immediately after the trauma. In other instances, it first appears after a latent period of hours, sometimes the next day. Cowell[25] termed these two varieties primary and secondary shock. In war wounds, secondary shock was far more common than primary shock; indeed, from the experiences of military surgeons summarized in Cannon's[22] book, it appears that primary shock was a rarity. I do not think that the discrepancy between primary and secondary shock is equally great in civilian practice. It is probable that the high incidence of secondary shock in military experience is due to the fact that the wounded man often bleeds slowly for a considerable period or has to be transported for a considerable distance in a stretcher exposed to cold, factors which bring on shock where it would be averted under the conditions of civilian practice. It was observed during the World War that the frequency of shock diminished with improvement in the means for transporting the wounded. Observations were recorded of recovery from primary shock followed by the development of secondary shock. Primary traumatic shock is discussed on page 651.

* For many details, the reader is referred to the classical monograph of Cannon,[22] based on extensive original investigation, and the recent lecture of Blalock,[14] summarizing his important contributions to the understanding of shock.

Pathogenesis of Secondary Traumatic Shock.—Much of our knowledge of the nature of peripheral circulatory failure is derived from studies, especially during the World War, on secondary traumatic shock. This work has crystallized into three main theories of the mechanism of the peripheral circulatory failure in secondary traumatic shock: (*a*) Vasomotor paralysis; (*b*) failure of the venopressor mechanism; (*c*) decrease in circulating blood volume While each of these theories has authoritative adherents, the evidence in favor of the primary significance of decrease in circulating blood volume seems practically conclusive The present status of the subject can perhaps be best elucidated by considering each of the theories in turn

Vasomotor Paralysis.—Beginning with the studies of Mitchell, Morehouse and Keen[83] during the Civil War, older clinicians almost universally attributed traumatic shock to damage to the vasomotor apparatus. The conception was that—in various ways according to the particular theory—the tone of the vasomotor apparatus is depressed with resultant relaxation of the peripheral blood vessels; in consequence, their capacity is so greatly increased that little blood is returned to the heart—"the patient bleeds to death within his own vessels." The theory was thus the same as that which, as seen below, probably applies to *primary* traumatic shock It was conceived that the most significant vasomotor relaxation occurred in the capacious splanchnic territory. Such a theory accounts very well for the cardinal features of shock—the collapsed peripheral veins, the low arterial pressure, and the cold skin. It also accounts for the similarities between the clinical pictures of shock and hemorrhage—in one case the "bleeding" is into the capacious splanchnic vessels, in the other to the exterior

Perhaps the best known theory of this gender is the *kinetic theory of Crile*,[26] developed over a period of forty years. He believes that the fundamental basis of shock is excessive stimulation of afferent nerves by physical trauma, pain, worry, fear, or infection. The stimuli call forth defensive responses by the organism through the intermediacy of the central nervous system, the suprarenal glands, and other organs If the stimuli are sufficiently intense and protracted, the defensive mechanisms are exhausted, which is manifested by shock. It is on the basis of this theory that Crile introduced his well-known procedures for preventing surgical shock by reducing the fear of the operation and the trauma of the operative procedure itself.

According to this theory, the circulatory phenomena which are at the basis of shock are due to the exhaustion of the vasomotor centers. Available evidence, however, indicates that the vasomotor center functions very well until late stages of secondary traumatic shock. The demonstration by Porter and Quinby[94] that

depressor reflexes can be elicited in an animal in shock showed that tonic activity of the vasomotor center is present, for if the vasomotor center were not functioning, it could not be depressed. Further evidence of the presence of vasomotor tone in shocked animals was afforded by the observation of Seelig and Lyon[106] that section of a nerve is followed by increase in blood flow through the part. Moreover, Mann[78] found that even in deep shock, asphyxia still produces a marked rise in arterial pressure—proof that the vasomotor center is able to increase its activity in response to an appropriate stimulus. Further studies have revealed that the tone of the vasomotor center is actually often increased until late stages of shock, for the peripheral arterioles are more constricted than prior to the onset of the shock. Such investigations were carried out by Erlanger, Gesell and Gasser,[33] and by Catell.[23] They estimated the vascular tone by measuring the rate of perfusion of salt solution introduced into the femoral artery of an animal which had been thrown into shock by manipulation of the intestines, muscle injury, or other procedures. The rate of perfusion frequently increased as the animal went into shock and the arterial pressure fell, indicating that the peripheral vessels were constricted. Only in the terminal stages did the rate of perfusion increase above the normal, showing that the peripheral vessels had relaxed, a phenomenon reasonably attributed to ischemia of the vasomotor center.

Observations on secondary traumatic shock in humans are in accord with these experimental findings. The pale, cold skin indicates that the cutaneous arterioles are not relaxed. And observations by various surgeons (Cannon[22]) who operated on patients with traumatic shock revealed that not only was splanchnic engorgement absent, but the viscera and peritoneum were pale.

It therefore seems clear that the vasomotor center is not exhausted and relaxation of the peripheral vessels is absent until the terminal stages of secondary traumatic shock. The diminished venous return to the heart characterizing the peripheral circulatory failure of secondary traumatic shock is not due to relaxation and increased capacity of the small vessels, and one must look elsewhere for the cause.

Henderson's Theory of Failure of the Venopressor Mechanism.—The conception that the circulatory failure of shock is due, not to heart failure, but to inadequate venous return to the heart is largely an outcome of the brilliant studies of Henderson,[60] pursued through three decades. That deficient venous return to the heart actually exists in peripheral circulatory failure would seem to be established by the low venous pressure. On the other hand, Henderson's views on the pathogenesis of the deficient venous return have met with much opposition.

Henderson has applied the term venopressor mechanism to the

totality of the forces which, superadded to what is left of the energy of the heart beat, serve to return the blood from the capillaries to the heart. He believes that the circulatory failure of shock is due to weakening of this mechanism. In his earlier studies, Henderson attributed failure of the venopressor mechanism to *acapnia*, *i. e.*, deficiency of carbon dioxide in the blood and tissues The conception, supported by much experimental work, was as follows: Pain, fever, general anesthesia, and other moments which induce shock do so through the intermediacy of hyperventilation. The hyperventilation dissipates the carbon dioxide of the body As a result of the deficiency of carbon dioxide, the venopressor mechanism functions poorly and the blood stagnates in the capillaries with consequent circulatory failure. We will not go into the details of the evidence adduced in favor of this hypothesis, because subsequent work (see Cannon[22] for a critique) showed that shock often occurs in the absence of hyperventilation, and can be produced experimentally despite the artificial maintenance of the carbon dioxide content of the blood at a high level Actually, the acapnia is probably a *consequence* of the circulatory failure due to the accumulation of lactic and other fixed acids as a result of decreased blood flow.

More recently, Henderson has arrived at the conclusion that the failure of the venopressor mechanism in shock is due to diminished tone of the musculature, both skeletal and smooth, that of the diaphragm being especially important. He believes that the tone of the musculature is an important factor in the regulation of the venous return to the heart. By thrusting a hypodermic needle into the middle of a muscle and allowing salt solution to run in, Henderson and his associates found that there is an internal pressure in a resting muscle of about 50 to 70 mm of water, which rises to 90 mm. or more when muscle tone is increased, and is absent when muscle tone is abolished. Henderson believes that this intramuscular pressure resulting from muscle tone plays an important part in forcing the capillary blood toward the heart. Further, he holds that the tone of the diaphragm and other muscles of respiration is an especially important part of the venopressor mechanism, for it helps in producing the negative intrathoracic and positive intra-abdominal pressures, which aid the venous return to the heart. In shock, according to Henderson, general muscle tone and hence intramuscular pressure as well as the function of the respiratory muscles are depressed, the consequence is that the blood stagnates in the periphery with resultant circulatory failure Henderson does not specifically describe the cause of the diminution in muscle tone which he regards as responsible for shock, but states that under such circumstances as illness, surgical operation, and anesthesias,

there is coördinated depression of muscle tone, volume of circulation and respiration.

The theory of Henderson is very interesting, but direct evidence of its validity has not yet been presented. It is conceivable that decrease in intramuscular pressure in shock may be a consequence of an empty state of the intramuscular blood vessels, due to the diminution in circulating blood volume described in the next section. Low intramuscular pressure would then be merely one of the symptoms of shock.

Decrease in Circulating Blood Volume.—The presence of low arterial and venous pressures in secondary traumatic shock immediately suggests the possibility that the volume of blood in active circulation is diminished.

That such is actually the case was shown during the World War by the splendid investigations of Keith.[64] Using Keith, Rowntree and Geraghty's dye method for determining the circulating blood volume, he found that this volume, as well as the circulating plasma volume, was consistently reduced in soldiers suffering from wound shock. The circulating blood volume ranged between 52 and 85 per cent and the circulating plasma volume between 62 and 90 per cent of the normal. Keith further found that the diminution in blood volume bore a definite relationship to the severity of the shock. With recovery, the blood volume returned to normal. Keith's findings have been confirmed by all who have studied the circulating blood volume in secondary traumatic shock in man. Gasser, Erlanger and Meek[46] and others have investigated the circulating blood volume in experimental traumatic shock in animals and found that it is also diminished There can therefore be no doubt that *diminution in circulating blood volume is a constant characteristic of secondary traumatic shock* Moreover, the best therapeutic results in traumatic shock have been attained by transfusion and other measures which increase the circulating blood volume.

There is thus very strong evidence that *decrease in circulating blood volume is directly responsible for the circulatory failure of secondary traumatic shock.* In the following, we shall first consider the effects of decrease in circulating blood volume on the circulation and then take up the problem of the connection between the trauma and the oligemia.

Effects of Oligemia on the Circulation.—Diminution in circulating blood volume decreases the venous return to the heart to the extent that it is not compensated by acceleration in the velocity of blood flow. However, the conditions in traumatic shock do not seem favorable for such compensation. The increase in the velocity of blood flow could be mediated only through reduction in peripheral resistance by dilatation of the arterioles, and we have seen that there is ample evidence that in secondary traumatic shock these

vessels are constricted until close to the end. Direct evidence that the oligemia of severe shock is not fully atoned for by more rapid blood flow is afforded by measurement of the cardiac output in animals with experimentally produced shock, which have revealed it to be greatly diminished (Blalock[14]). While I am not acquainted with measurements of cardiac output in human traumatic shock,* the other features of the circulation are so nearly identical with those of experimental shock that similar decrease in cardiac output is doubtless present.

Utility of Vasoconstriction in Shock.—Perhaps the most important adaptation of the circulation to the diminished cardiac output thus resulting from the oligemia of traumatic shock is the peripheral vasoconstriction mentioned above. This acts in two ways.

1. The diminished cardiac output, of course, tends to lower the arterial pressure. To a certain extent, this is counteracted by the peripheral vasoconstriction. It was mentioned above that in the initial stage of traumatic shock the arterial pressure may be maintained or even elevated; evidently the vasoconstriction atones for the diminution in cardiac output. But sooner or later the diminution in cardiac output gains the upper hand and the arterial pressure falls, though not to as low levels as if the peripheral arterioles were not constricted.

2. The peripheral vasoconstriction results in an alteration in the distribution of blood which is favorable to the survival of the organism. One of the means by which adequate blood flow to an active organ is provided is by vasodilatation in that organ and coincident vasoconstriction in other parts, with the result that blood is diverted from the inactive to the active organs. The same mechanism apparently functions when the cardiac output is diminished by oligemia and tends to maintain a volume of blood flow through the heart and central nervous system sufficient for the survival of the organism. To accomplish this as far as possible, the arterioles in the extremities and splanchnic area are, as described above, constricted. The result is that a relatively high proportion of the diminished cardiac output is diverted to the parts where it is most necessary, *i. e.*, the central nervous system and heart.

The operation of these mechanisms is beautifully illustrated in experiments carried out by Gesell.[47] He found that even though a reduction of 10 per cent in the circulating blood volume of an animal did not cause reduction in arterial pressure, it did result in a decrease of 60 per cent in the blood flow through the submaxillary gland. The diminution in blood flow through the submaxillary gland could have been due only to constriction of the vessels supplying it. By thus cutting down the blood flow through the peripheral

* However, Freeman, Shaw and Snyder[41] have demonstrated greatly decreased blood flow through the hand in human surgical shock

organs disproportionately more than the circulating blood volume is reduced, the twofold purpose is served of maintaining the arterial pressure and diverting blood to the more vital organs. This is evidently what occurs in human traumatic shock. The reason that the extremities of the patient are so pale and cold, and the veins so empty, is largely that the vessels of the periphery are constricted in the effort to divert as large a fraction as possible of the small cardiac output to the parts where it is most vitally needed.

The protective accomplishment of peripheral vasoconstriction in oligemic shock is well brought out in the experiments of Freeman[40] and his associates They found that sympathectomized dogs, who cannot effect such vasoconstriction, were unable to tolerate as large hemorrhages as normal controls. The blood pressure also fell more steeply and further in the sympathectomized animals.

Experiments show that if shock persists long enough, the constricted arterioles relax, probably largely as a result of deficient blood flow through and consequent weakening of the vasomotor center. With this, the compensations just described cease to function and the blood pressure falls to mortal levels.

The Mechanism and Cause of the Decrease in Circulating Blood Volume.—In the foregoing, the pathogenesis of the symptoms of secondary traumatic shock has been traced as follows: The symptoms are to be attributed to diminution in cardiac output. The fall in cardiac output, in turn, is the result of decrease in the venous return to the heart. And, finally, the diminution in venous return to the heart is due to a decrease in circulating blood volume.

We now come to the fundamental question: How does trauma decrease the circulating blood volume? With this question, the firm basis of established fact is left, and the realm of theories entered.

Traumatic Toxemia and the Histamine Theory.—During the World War, Quénu[97] and other surgeons were impressed by the fact that traumatic shock usually does not become manifest until several hours after the injury—for which reason the term secondary shock was introduced. Considerable clinical evidence was adduced which seemed to show that factors facilitating absorption from the traumatized tissue favor the development of shock, while moments hindering absorption tend to prevent shock. Cases were reported in which shock appeared only after a tourniquet had been released from a *mangled limb.*

The conception was thus attained that toxic products are formed or liberated in the injured tissues, which produce shock when they attain a sufficient concentration in the general circulation—traumatic toxemia.

Important and what then seemed almost conclusive evidence of the existence of traumatic toxemia was advanced by Bayliss and Cannon.[7] They produced shock by crushing muscles in the hind

limbs of dogs and cats. They found that shock does not appear if the blood vessels supplying the injured limbs are tied, but develops if the ligature is released, and is favored by massaging the injured area. These observations seemed most readily explicable on the basis that a shock-producing substance is liberated in the damaged tissue and brings about its effect through entry into the general circulation. In the search for the shock-producing substance, observations were made which were taken to indicate that the substance in question lowers the circulating blood volume and thus produces shock through two mechanisms: (1) Dilatation of capillaries, within which blood stagnates so that it contributes little or nothing to the active circulation, (2) increase in the permeability of the capillaries, so that plasma is extravasated

Capillary Dilatation.—During the World War, Cannon noted that in traumatic shock the red cell count of the blood in the capillaries of the skin is notably higher than that of the venous blood. In normal subjects, he found that the erythrocyte count of the capillary and venous bloods does not differ by more than 3 per cent On the other hand, Cannon showed that in severe traumatic shock the red cell count of the capillary blood is often as much as 2,000,000 per c.mm. higher than that of the venous blood. Further, he found that the difference between the capillary and venous erythrocyte counts roughly parallels the severity of the shock and disappears with improvement.

The concentration of erythrocytes is not limited to the capillaries of the skin. Erlanger and his associates found that in experimental shock the capillaries and venules of the intestinal villi are packed tight with red corpuscles. More recently, Moon and Kennedy[85] have carried out a careful study of the histology of various organs of dogs in whom shock had been produced by trauma or the introduction of extracts of normal or traumatized muscle into the peritoneum. The animals developed a clinical picture and concentration of the blood identical with that of human traumatic shock They found that in various organs—the lungs, gastro-intestinal tract, liver, kidneys, etc.—the capillaries were markedly dilated and packed tight with red cells. There were also numerous capillary hemorrhages, and edema could often be demonstrated microscopically. They also observed similar lesions in a woman who succumbed to postoperative shock, as well as in sections of organs of soldiers who had been victims of traumatic shock during the World War. On the basis of these observations, Moon and Kennedy believe that dilatation and engorgement of capillaries accompanied by capillary hemorrhages and edema constitute the characteristic lesion of shock.

The above observations demonstrate that widespread dilatation of capillaries with stagnation of red cells within them occurs in

secondary traumatic shock. Blood thus stagnated in dilated capillaries is removed from currency almost as effectively as if it had been extravasated, for the circulation through the dilated capillaries is so slow (page 65) that they contribute very little to the venous return to the heart. If Congo red is injected or carbon monoxide inhaled, it mixes so slowly with the stagnated blood within the dilated capillaries (page 62) that the circulating blood volume measured by these methods is found to be correspondingly reduced.

Of special interest is Moon's finding that, despite widespread capillary dilatation, the spleen is small and maximally contracted in traumatic shock. This shows that the splenic reservoir of blood has been emptied into the general circulation, and that the diminution in circulating blood volume is not even partly due to storage of blood in the spleen.

Increase in Capillary Permeability.—It has long been known that the blood is concentrated and highly viscous, and the red cell count increased, in various forms of clinical and experimental shock. Taken in conjunction with the decreased circulating plasma volume (*page 630*), *this finding shows that plasma fluid is extravasated in* traumatic shock. The further finding that the concentration of the plasma proteins is not increased in secondary traumatic shock indicates that the fluid which passes from the blood stream consists not only of water and crystalloids but that also plasma proteins pass out. These observations were interpreted by Cannon and his associates as indicating that in traumatic shock there is widespread increase in the permeability of the capillaries which results in transudation of plasma and consequent fall in circulating plasma volume; the alternative explanation of local loss of plasma at the site of trauma (page 637) was not accepted at the time.

In his recent monograph, Moon[84] has strongly championed the predominant importance of dilatation and increased permeability of the capillaries in the production of traumatic and other forms of shock.

The Histamine Theory—In the foregoing, we have seen that the adherents of the theory of traumatic toxemia believed that the hypothetical substance liberated from the traumatized tissue is one which depresses circulating blood volume through the twofold mechanism of (1) producing capillary dilatation with consequent stagnation of red corpuscles, and (2) increasing the permeability of the capillaries with resultant extravasation of plasma. Of course, these might be merely two aspects of the same process, for it is believed that, at least under certain circumstances, the permeability of the capillary wall increases *pari passu* with dilatation (Krogh[69]).

It seemed that histamine or some histamine-like body might well be the hypothetical shock-producing substance defined by these

effects. The classical investigations of Dale, Laidlaw and Richards[27] showed that the injection of comparatively small amounts of histamine into carnivora produced the characteristic circulatory changes of shock. They found that in histamine shock the capillaries are dilated and packed with red cells and their permeability is increased so that plasma passes into the tissue spaces; as a result of these changes, the circulating blood volume is diminished and the venous return to the heart is decreased *

These observations leave no doubt that the circulation of adequate concentrations of histamine or histamine-like bodies can reproduce the clinical picture of secondary traumatic shock in all its essential details. However, proof is not yet available that histamine or any other substance with similar properties actually circulates in traumatic shock, or even that they are present in high concentration in traumatized tissues While some older experiments seemed to point in this direction, more recent careful studies by Smith[107] and by Parsons and Phemister[89] did not reveal that toxic substances actually enter the blood stream from the injured tissues. Roome and Wilson[103] found that extracts of a traumatized limb of a dog do not produce fall in blood pressure or death when perfused into another animal Attractive though it is, the theory that traumatic shock is due to the circulation of histamine or any other body resulting from tissue damage with similar action on the capillaries is without support which seems convincing to the writer (*cf.* Moon[84] for an able presentation of the opposite view).

The Theory of Suprarenal Insufficiency.—The conception has repeatedly been advanced that traumatic shock is due to inhibition of secretion by the suprarenal glands. The earlier theories attributed the low arterial pressure in traumatic shock to deficient secretion of epinephrin by the chromaffin cells of the medulla. But since the physiological rôle of epinephrin in maintaining the tone of the arterioles has become more than doubtful, this theory seems *to lack tangible support.*

More recently, attention has been diverted to the suprarenal cortex. As will be seen on page 648, the circulatory failure during the crises of Addison's disease and in adrenalectomized animals is identical with that of traumatic shock. In both traumatic shock and suprarenal insufficiency, the circulatory failure is manifested by deficient venous return to the heart conditioned by decrease in

* Pick and Mautner attribute the diminution in circulating blood volume and venous return to the heart that are produced in the dog by histamine to constriction of the hepatic veins (page 66) While this mechanism functions in some experimental animals, its significance in man is still *sub judice* And regardless of whether or not histamine constricts the hepatic veins in man, the marked enlargement of the liver that would be expected to result from significant obstruction of the hepatic veins is not observed in human traumatic shock I have several times carefully palpated the right upper quadrant in severe shock, but have been unable to feel the liver

circulating blood volume. Because of this and other analogies between the pictures of traumatic shock and suprarenal insufficiency, Swingle[114] and his co-workers attribute traumatic shock to suprarenal insufficiency. However, further evidence is needed before this theory can be accepted. All that has been shown is that circulatory failure in both suprarenal insufficiency and traumatic shock is due to a decrease in circulating blood volume. But this does not prove that the circulatory failure of traumatic shock is due to suprarenal insufficiency. Other agents can also produce shock through the intermediacy of decrease in circulating blood volume as is shown, for example, by histamine shock. Recent observations (page 804) of therapeutic aid from the administration of an adrenal cortical hormone in the closely related surgical shock afford no evidence that adrenal insufficiency is concerned in the causation of the shock; any measure which elevates blood volume tends to help all varieties of oligemic shock.

Sympathetic Hyperactivity.—Freeman[39] has brought up the possibility that traumatic shock results from prolonged hyperactivity of the sympathetic nervous system. Freeman points out that the factors—hemorrhage, cold, fear, pain, asphyxia, infection, low blood pressure—which produce or aggravate shock are likewise stimulants of the sympathetic nervous system, as shown by vasoconstriction or by hypersecretion of epinephrin. He produced prolonged hyperactivity of the sympathetic nervous system by infusion of epinephrin in physiological amounts or by inducing the spontaneous emotional activity of the pseudoaffective state. The sympathetic hyperactivity thus produced was accompanied by decrease in the circulating blood volume, both plasma and corpuscles being affected. Freeman found evidence that the decrease in circulating blood volume was due to vasoconstriction, for he observed that in similar experiments the blood volume did not diminish if vasoconstriction was inhibited by ergotoxin or prevented by complete sympathectomy. How the vasoconstriction in these experiments causes the decrease in circulating blood volume is hypothetical. That anoxemia increases the permeability of the capillaries is known and this may be the link. Further, Freeman cites evidence that cutting down of arterial blood flow can result in capillary dilatation with stagnation of red cells, which are thus withdrawn from currency.

The suggestion that sympathetic hyperactivity may cause shock through the intermediacy of vasoconstriction and the consequent decrease in circulating blood volume is in such good accord with the circumstances under which shock occurs and its clinical manifestations, that it merits further investigation. The conception clarifies the cases of traumatic shock in which the fall in blood pressure is preceded by a rise, a phenomenon which is perhaps more common than is generally appreciated. But as yet it is only a theory.

Local Extravasation of Blood or Plasma.—In an important series of experiments, Blalock[15] has supported the thesis that traumatic shock is due to the local extravasation of blood or plasma in the injured area, which decreases the circulating blood volume and thus causes circulatory failure. He traumatized one posterior extremity of an experimental animal and measured the amount of whole blood or plasma that was extravasated into the tissues by comparing the weight with that of the opposite extremity Blalock found that in animals which went into shock, the amount of blood or plasma extravasated was equal to that which was required to produce shock by bleeding or removal of plasma (plasmapheresis) Similarly, when he induced shock by traumatizing the intestines or by burns, the volume of plasma extravasated was correspondingly large. According to Blalock's theory, the latent period after injury that precedes the development of secondary traumatic shock is the time required for sufficient blood of plasma to pass out from the *damaged vessels.*

Blalock has made a notable contribution to knowledge of traumatic shock by bringing out the magnitude of the loss of blood or plasma that may occur at the site of the shock-producing trauma He would appear to have established that in the forms of experimental shock with which he worked, the drain on the circulating blood volume due to the local loss of plasma or blood is the fundamental cause of the circulatory failure. It would seem that this explanation also holds in at least many instances of clinical traumatic shock. However, the question arises whether there is not also some additional factor which interferes with the restoration of the circulating blood volume by resorption of fluid from the tissues. Blalock believes that when fluid is thus resorbed it raises the capillary pressure and thus increases the transudation in the traumatized area so that the circulating blood volume does not rise Nevertheless, if the fluid exchange between blood stream and tissues functioned as usual, one would expect that tissue fluid would be resorbed until the tissues were severely dehydrated and only then would the circulating blood volume fall as a result of the drainage of plasma in the traumatized area. This is what happens in, for example, the shock of high intestinal obstruction. But there are cases of early though severe traumatic shock with low circulating blood volume in which the skin, at least, does not appear notably dehydrated. Moreover, the plasma proteins may not be depressed in traumatic shock, which it is difficult to reconcile with drainage of plasma at the site of trauma and corresponding inflow of tissue fluid, which is poor in protein. In view of these considerations, the possibility must be borne in mind that the depression in circulating blood volume in traumatic shock is due not only to drainage of plasma in the traumatized area but also to some unknown factor

which interferes with the resorption of fluid from the tissue spaces into the blood stream.

Even the foregoing brief survey will serve to indicate that the mechanism of the decrease in circulating blood volume that mediates the symptoms of secondary traumatic shock has not been unequivocally determined. Drainage of plasma in the traumatized area, generalized seepage of plasma as a result of increased permeability of the capillaries, capillary dilatation with pooling of red cells, and other mechanisms may be concerned, but their relative importance remains to be established; it may vary in different forms of traumatic shock.

HEMORRHAGIC SHOCK

Profuse hemorrhage can produce the typical clinical picture of shock. This is so common that whenever an individual goes into shock without obvious cause, or some time after an operation, internal bleeding is one of the first possibilities that enter the physician's mind Often, trauma and hemorrhage combine to produce shock.

The constitutional effects of hemorrhage result in two ways: through decrease in circulating blood volume, and through decrease in the hemoglobin content of the blood. Clinically, and from the point of view of circulatory dynamics, three groups of cases can be recognized:

1. Those in which neither the volume nor the hemoglobin content of the blood is lowered sufficiently to exert more than a transitory effect on the dynamics of the circulation.
2. Those in which the circulating blood volume is restored but the hemoglobin content of the blood is severely depressed.
3. Those in which the circulating blood volume is diminished enough to produce shock. There may also be manifestations of hemoglobin deficiency.

Hemorrhage With Only Transitory Effect on the Circulation.—If the amount of blood lost is comparatively small—up to several hundred cubic centimeters in a healthy adult—the circulation quickly returns to normal. When the blood is drawn no faster than the rate at which it can be obtained from a peripheral vein, as during a transfusion, measurement of the blood pressure and heart rate while 300 or 500 cc. of blood are being removed may show practically no change in a donor who is not apprehensive. But when the hemorrhage is more rapid, as in bleeding from a large artery, there is a transitory fall in blood pressure. This was illustrated in the classical investigations of Worm-Mueller.[123] He removed from a dog within ten seconds a quantity of blood equal to a little less than 1 per cent of the body weight, and found that while the arterial pressure fell from its previous level of 130 to 57 mm., one hundred

and fifty-six seconds later it had risen to 151 mm. A second bleeding was carried out at this time and finished within eight seconds with the result that the arterial pressure fell to 92 mm., to return to 129 mm. at the end of one hundred and twenty-two seconds It was only after four such bleedings, each of 1 per cent of the body weight and carried out at intervals of two to four minutes, that the arterial pressure did not rapidly recover and the animal went into fatal shock.

This almost immediate restoration of the arterial pressure after loss of moderate quantities of blood is due to vasoconstriction in the periphery (page 628). That it is not due to an inflow of fluid into the blood stream was shown by the observations of von Limbeck.[119] He found that one minute after bleeding a dog of about one-third of the volume of blood in the body the blood pressure had returned almost to its previous level, the red cell count at this time had not dropped, evidence that a significant volume of tissue fluid had not yet entered the blood stream. Even at this early stage, however, mobilization of fluid from the tissue spaces and erythrocytes from the spleen and other reservoirs has started, and as the circulating blood volume is thus gradually restored the vasoconstriction becomes no longer necessary for the maintenance of the arterial pressure. If the amount of blood lost is small, the red cells mobilized from the reservoirs may be sufficient to keep the erythrocyte count at the previous level But with any considerable loss of blood, sufficient red cells are not available in the reservoirs and the circulating blood volume is made up preponderantly by fluid from the tissue spaces, with resultant fall in the erythrocyte count However, the amount of tissue fluid available in even the healthy organism is not unlimited. Rous and Wilson[105] found in rabbits that after about one-half the blood volume had been removed by successive bleedings, tissue fluid was no longer available to restore the circulating blood volume.

Hemorrhage With Resultant Anemic Manifestations.—If a larger volume of blood is lost more slowly, or there is repeated or continuous small bleeding, the circulating blood volume is usually maintained by fluid from the tissues or ingestion For this reason, there are no symptoms of shock. However, the hemoglobin content of the blood falls, necessitating the important circulatory adjustments for decreasing oxygen-carrying capacity which are discussed on page 575.

Hemorrhagic Shock.—Sufficiently copious and rapid bleeding results in shock, *i. e.*, the consequences of circulatory failure immediately conditioned by deficient venous return to the heart. The deficient venous return is immediately obvious from the collapsed state of the superficial veins. Very often, the hemorrhage is combined with trauma or some other factor in the production of the

shock. But in other instances, such as hemorrhage from a peptic ulcer or a tuberculous cavity, shock results purely from the loss of blood.

There can be no doubt that the cause of hemorrhagic shock is decrease in circulating blood volume. This was shown clearly by Robertson and Bock's[99] extensive studies during the World War. They found that while a small and sometimes even a considerable decrease in circulating blood volume due to hemorrhage might be compensated by vasoconstriction so that the arterial pressure was maintained and shock did not appear, more marked fall in circulating blood volume was present when hemorrhage resulted in shock. They further showed that in hemorrhages larger than those compensated by vasoconstriction, there was rough parallelism between fall in arterial pressure and diminution in circulating blood volume In a number of Robertson and Bock's cases, the circulating blood volume was less than 60 per cent of the normal, in one instance being only 54 per cent of normal. The latter value probably approaches the lowest circulating blood volume compatible with survival; it has been found that hemorrhage of about one-half the blood volume is quickly fatal.

Little need be said about the clinical picture of hemorrhagic shock, which is practically identical with that of traumatic shock In cases of trauma with bleeding, the hemoglobin content of the blood may afford information regarding the relative importance of the two factors in the genesis of the shock; hemorrhage causes the hemoglobin concentration to fall as the tissue fluid dilutes the blood, while the effect of trauma is to raise the hemoglobin content for a considerable time because of loss of plasma. Moreover, in hemorrhagic shock transfusion is usually a sovereign remedy and infusion of salt solution often also causes very striking improvement. While these measures are also often very helpful in traumatic shock, it is unusual for them to have such spectacularly favorable results as in pure hemorrhage.

POSTOPERATIVE SHOCK

A symptom complex identical with traumatic shock may be precipitated during or more often shortly after a surgical operation The longer the operation and the more extensive the procedure, the more likely is the development of shock. Excessive handling and instrumentation of tissues and immoderate loss of blood are especially apt to lead to shock. The latter is perhaps most common after abdominal operations involving protracted manipulation of the intestines. Operations under general or spinal anesthesia are more often complicated by shock than those under local anesthesia; and of the general anesthetics, ether and chloroform appear to be decidedly more dangerous in this regard than gas oxygen.

The causation of postoperative shock is obviously to be sought along lines similar to those of traumatic shock. We have already mentioned Crile's view that surgical shock is due to overstimulation and subsequent exhaustion of the nervous centers due to fear, pain, etc. Henderson[60] held that surgical shock is due to hyperventilation incidental to the induction of the anesthetic and other factors, the hyperventilation, according to Henderson, depletes the carbon dioxide content of the blood and tissues and thus reduces the venous return to the heart. More recently, Henderson has advanced the theory that anesthesia and operation depress the tone of the muscles, which diminishes the venous return to the heart and thereby produces circulatory failure, and at the same time predisposes to postoperative pulmonary atelectasis because of the relaxation of the diaphragm and other respiratory muscles The theories of Crile and Henderson have already been discussed (page 627)

While Henderson's theories of the significance of carbon dioxide depletion and diminished muscle tone remain very much *sub judice*, his conception of diminished venous return is well established *Postoperative shock is a typical form of peripheral circulatory failure manifested by diminished venous return to the heart* This is proved by the low venous pressure and the marked diminution in circulating blood volume that have been shown to be present by Riessinger and Schneider,[98] Ewig and Klotz,[34] and others I have also observed abnormally low venous pressure and circulating blood volume in circulatory collapse following operation. Unless there is profuse bleeding, the decrease in blood volume is due preponderantly to loss of plasma, for the red cell count and hematocrit rise Experimentally, Riessinger and Schneider found that when they opened the abdomen and manipulated the intestines so that shock resulted, the circulating blood volume was depressed The best therapeutic results in postoperative shock are attained by measures which tend to elevate the circulating blood volume.

The oligemia which, when sufficiently pronounced, results in surgical shock appears to be an exaggeration of a decrease in blood volume that occurs in almost all major operations under general anesthesia. Thus, Stewart and Rourke[110] found that the plasma volume fell in 14 of 16 patients undergoing major operations under ether anesthesia lasting one to three hours, the average fall was 14 9 per cent.

Doubtless a consequence of the oligemia developing during extensive surgery and protracted anesthesia is a fall in *cardiac output* In 9 patients undergoing such procedures, Snyder[109] found the cardiac output during recovery from etherization an average of 41 per cent below the preoperative level.

The cause of surgical shock is thus to be sought in factors which lower the circulating blood volume, and consequently the cardiac

output, in almost all extensive operations, and are exaggerated when shock develops. They are probably multiple and different in individual cases. Hemorrhage is, of course, especially potent in this regard. In almost every operation, especially under general anesthesia, there are a number of factors which tend to dehydrate the body. Among these are profuse perspiration, hyperventilation with resultant increase in water lost in the expired air, and frequently vomiting. Blalock points out the significance of excessive preliminary catharsis in this regard. How great is the dehydration that commonly occurs during and after operations has been brought out by the investigations of Coller and Maddock[24] and MacFee and Baldridge.[76] The latter investigators found that, despite fluid intake of about 2500 grams, the body weight averages 1400 grams less twenty-four hours after tonsillectomy than before the operation. The loss is, of course, nearly all water, and the blood doubtless participates in the general dehydration with consequent decrease in circulating blood volume. Excessive handling of the intestines causes extravasation of plasma, which in Blalock's[12] experiments was sufficient to lower the circulating blood volume strikingly The effects of the anesthetics are also of importance. The mere opening of the peritoneum has been observed often to result in transitory drop in blood pressure; this has been attributed to a nervous reflex, but the altered mechanical conditions for the venous return to the heart resulting from the opening of the peritoneum may also be concerned. In most instances of surgical shock, there is probably summation of several factors tending to lower the circulating blood volume and perhaps also decrease the venous return to the heart through other mechanisms.

PERIPHERAL CIRCULATORY FAILURE DUE TO VOMITING OR DIARRHEA

Immoderate and sufficiently protracted loss of the contents of the stomach or intestines results in shock. There is pale, sweating skin, cold extremities, oliguria, low arterial pressure, and collapsed veins with low venous pressure. The picture is thus practically identical with that of traumatic shock, although the evidences of dehydration in the skin, mucous membranes, and eyeballs usually become more pronounced. Concentration of the blood is indicated by elevation of the red cell count and hemoglobin percentage. Chemical examination of the blood reveals nitrogen retention, hypochloremia, and, as Gamble and Ross[45] showed, depression in content of fixed base. There may be alkalosis or acidosis, depending on the character of the fluid lost from the body.

Among the clinical conditions presenting this picture of shock

due to loss of gastric or intestinal contents, the following may be mentioned:

1. Vomiting due to pyloric or intestinal obstruction.
2. The gastro-intestinal disorders of infancy accompanied by vomiting or diarrhea.
3. Various forms of vomiting and diarrhea in adults—gastroenteritides, pernicious vomiting of pregnancy, uremic vomiting and diarrhea, etc.

I have also seen classical shock as a result of a biliary fistula; the sodium content of the plasma was depressed and the shock was quickly relieved by the administration of sodium chloride.

The studies of Gamble,[43] Marriott,[79] Atchley,[4] and others have shown that in all these conditions the pathogenesis of the shock is similar. Vomiting or diarrhea leads to loss of large quantities of water and dissolved salts. Because of the condition of the gastro-intestinal tract, the replacement of water and salts is impeded. This is especially true in infants who also lose large quantities of fluid through the skin The result is that the organism becomes dehydrated and the circulating blood volume diminished as part of the general dehydration. The oligemia, in turn, diminishes the venous return to the heart with consequent circulatory failure and shock. In some instances (*e. g*, cholera), the blood is so highly concentrated that the resistance to flow resulting from the great viscosity may be an accessory factor in diminishing the venous return to the heart This conception of the pathogenesis of shock resulting from vomiting or diarrhea is supported by the splendid therapeutic results often obtained by the intravenous infusion of large volumes of salt solution, a procedure that has been in use for a century in the treatment of cholera.

It is to be emphasized that loss of salts plays an especially important part in the pathogenesis of the dehydration underlying the shock. Gamble and Ross believe that the water content of the organism is largely a function of the quantity of dissolved electrolytes in the body (page 647) The consequence is that unless the salts are replaced, dehydration cannot be alleviated by the supply of water. Formerly, the principal stress was laid on the loss of chloride. However, Gamble and Ross have shown that vomiting and diarrhea also produce notable waste of sodium, and that this is even more significant for the total electrolyte content of the blood than is loss of chloride. For when chloride is lost, the total concentration of acid radicals can be maintained by lessened elimination of carbon dioxide in the expired air, with the result that the concentration of bicarbonate rises to the extent that chloride falls. But when sodium is lost, the sum of the acid radicals in the blood must decrease correspondingly in order to maintain the balance of acid and base The result is that the total electrolyte content of

the blood and tissues falls sharply and dehydration is the consequence. It is important that the significance of the loss of salts be appreciated, for often much better therapeutic results are obtained by the administration of hypertonic than of physiological salt solution—a fact long ago pointed out in the case of cholera by Rogers.[100]

The fundamental rôle of loss of water and salt in the production of circulatory failure following vomiting or diarrhea has long been especially well realized in the instance of cholera, where the thickening of the blood and the desiccation of the tissues are so marked as to force themselves on the observer. "The severity of the cholera attack is in proportion to the loss of fluid and salts from the blood" (Rogers[100]) Much more slow was realization that the constitutional manifestations of pyloric and intestinal obstruction, and those of the gastro-intestinal disturbances of infancy, are likewise largely those of shock due to dehydration and decrease in circulating blood volume. Numerous investigations were carried out in the effort to show that these constitutional symptoms were due to the absorption of some hypothetical toxic body from the lumen of the gut. Darrow and Buckman[28] and McIntosh[82] and his associates showed the great frequency of decrease in circulating blood volume in the diarrheas of infancy. Of course, it is possible that in low intestinal obstruction, symptoms may also result from the absorption of toxic bodies from the putrefying contents. But it should be remembered that even though there is little vomiting in such cases, large amounts of fluid and salts may be contained in the dilated intestinal loops and lost to the economy as effectively as if they had been vomited. Within thirty hours after pyloric obstruction in the rabbit, an animal which does not vomit, Gamble and McIver[44] found that several times the total initial content of the plasma in water, fixed base, and chloride entered the stomach

PERIPHERAL CIRCULATORY FAILURE IN DIABETIC ACIDOSIS

Typical peripheral circulatory failure may develop in the course of diabetic acidosis Nowadays, indeed, it is mostly through the intermediacy of circulatory collapse that diabetic acidosis leads to a lethal outcome. Although the older investigators recognized a "cardiovascular coma," it is only since the introduction of insulin that the great significance of circulatory failure in determining the outcome of diabetic coma has been adequately appreciated. The importance of circulatory collapse became evident when cases were observed in which treatment with insulin had cleared the urine of glucose and ketone bodies and restored the sugar and bicarbonate of the blood to normal, and nevertheless the patient succumbed to circulatory collapse In such instances, it does not suffice to treat

the metabolic disturbance alone, but it is also necessary to take measures against the circulatory collapse.

Peripheral circulatory failure most often develops in diabetics after a protracted period of acidosis. However, it may also result, though much less often, from acidosis setting in acutely as a result of an infection or the cessation of insulin.* Most often, the sequence of events is that the patient goes into pre-coma or coma first and the symptoms of circulatory insufficiency develop a few days later. But there are also cases in which circulatory collapse is the first indication of the acidosis. It was mentioned above that the acidosis may be removed by insulin and yet circulatory collapse persist or first develop. Such patients may be fully conscious and yet in severe circulatory failure.

The clinical picture is that of diabetic acidosis plus that of typical shock as already described—restlessness going on to apathy and coma, thirst, vomiting, sunken features, soft eyeballs, inelastic skin, feeble and rapid pulse, and collapsed superficial veins. While Kussmaul breathing may be present, it is often absent.

The most important diagnostic sign of circulatory collapse in diabetic acidosis is fall in arterial pressure, which may develop and progress rapidly. It is just as important—often more important—to measure the arterial pressure in pre-coma or coma as it is to follow the chemical changes in the urine and blood. Fall in blood pressure calls for immediate treatment of the circulation, and the situation is serious if the arterial tension drops below 80 mm.

There is oliguria, which may approach anuria. The diminution in urinary volume generally results in nitrogen retention in the blood. The non-protein nitrogen of the blood may mount to 100 or 200 mg. per cent. It is because of the nitrogen retention that many cases of diabetic coma were formerly thought to be precipitated by renal insufficiency. However, there can be no doubt that the oliguria is purely a consequence of the circulatory failure. This is evidenced by the immediate increase in urinary volume and decrease in azotemia that follows successful treatment of the circulatory failure That the concentrating ability of the kidney is unimpaired in many cases is shown by the high specific gravity of the urine. In other instances, the specific gravity of the urine is fixed around 1.010 despite pronounced azotemia. The impairment of renal function thus demonstrated is probably a consequence of the circulatory

* In a recent case at Mount Sinai Hospital in which acute coma and circulatory collapse were ushered in by violent epigastric pain, acute pancreatitis was found at necropsy, presumably, the acute pancreatitis (p 652) abetted the diabetic metabolic disturbance in the pathogenesis of the shock and explained the complete inefficacy of the therapy Recent observations by Root[1H] indicate that such a sequence of events may be more common than has generally been realized Further observations are needed to show how often epigastric pain preceding diabetic coma is due to pancreatic necrosis

failure with its entailed diminution in volume of blood flow through the kidney (page 623), for the concentrating power is promptly restored with improvement of the circulation.

The manifestations of dehydration are more pronounced when circulatory collapse results from diabetic acidosis than in traumatic or hemorrhagic shock This is, of course, due to the fact that dehydration precedes the onset of circulatory failure and is indeed the prime cause of the latter. The most obvious evidences of dehydration are the shrunken state of the superficial tissues and the well-known softness of the eyeballs

It should be borne in mind that diabetic acid intoxication is often accompanied by epigastric or other abdominal pain. The circulatory collapse of acidosis should not be confused with the shock of coronary thrombosis, which is frequent in diabetics. I have known difficulties in this differential diagnosis.

Pathogenesis.—That the circulatory collapse of diabetic acidosis is a form of peripheral circulatory failure and results in diminished venous return to the heart is proved by the collapsed state of the superficial veins and the low venous pressure. I have several times observed the pressure in an antecubital vein to be about 1 cm. of water.

The diminished venous return to the heart results from decrease in circulating blood volume, *i. e.*, the circulatory collapse of diabetic acidosis is a form of oligemia. It has long been known that in these cases the blood is viscous and the red cell count and hemoglobin content are increased over their previous values. Widal[121] and Peters[92] and their respective associates have also found that the concentration of the plasma proteins generally rises in diabetic acidosis and falls with improvement. These findings point to concentration of the blood as a result of decrease in circulating plasma volume. That the circulating blood volume is actually decreased in severe diabetic acidosis, and returns to normal with disappearance of the acidosis, has been shown by the investigations of Harrop, Chang and Schaub[57] with the carbon monoxide method of determining circulating blood volume. They found that only the circulating plasma volume is diminished in acidotic diabetics with no essential change in the red cell volume. Harrop and his associates made no measurement in actual coma, but there can be no doubt that in this state the decrease in circulating blood volume is much more pronounced. That the decrease in circulating blood volume is the actual cause of the circulatory failure is indicated by the splendid therapeutic results that are generally attained by large intravenous infusions.

How the acidosis results in the decrease in circulating blood volume is not entirely settled. Doubtless, the oligemia is fundamentally part of the general dehydration of the organism that results

from the protracted polyuria and may be abetted by vomiting, sweating, and diarrhea. Harrop, Chang and Schaub also point out the large amount of water that may be lost in the expired air when there is Kussmau' breathing Discussion will not be attempted of the complicated and as yet largely obscure mechanisms through which loss of water results from the disturbance in carbohydrate metabolism and the resulting acidosis and other alterations in the electrolyte pattern of the blood and tissues; for many details, the reader is referred to the studies of Loeb, Atchley, *et al.*,[74] Peters *et al.*[93] and Blum and Van Caulaert.[17] It will merely be recalled that acidosis tends to promote diuresis, as is applied in the use of ammonium chloride and other acidifying salts. Moreover, ketogenic acidosis tends to deplete the fixed base of the body to the extent that the acids excreted in the urine are not matched by ammonia formed by the kidneys. And the sum of the bicarbonate plus the chloride concentrations in the blood is depressed, a fall that is doubtless paralleled in the tissues. In view of these findings, it may be accepted that the total dissolved electrolyte content of the body is diminished in severe diabetic acidosis. And according to Gamble and Ross,[45] "It is therefore probably permissible to postulate a close dependence of the volume of body water on the total quantity of dissolved electrolytes which the body contains" These considerations would indicate that "demineralization" is probably the prime cause of the dehydration of the organism in severe diabetic acidosis, of which decrease in circulating blood volume and consequent peripheral circulatory failure are one aspect. Such a conception also clarifies the necessity for administering large quantities of sodium chloride with the fluid given in the treatment of peripheral circulatory failure due to diabetic acidosis (page 808).

In addition to the loss of water from the body, the observations of Peters[92] and his associates on the plasma proteins in diabetic acidosis indicate that other factors, which displace fluid from the blood to the tissues, may also be concerned in reducing the blood volume.

PERIPHERAL CIRCULATORY FAILURE IN ADDISON'S DISEASE

Peripheral circulatory failure dominates the acute exacerbations of Addison's disease, which are characterized by intensified asthenia, gastro-intestinal and sometimes mental symptoms, fall in blood pressure, rise in the non-protein nitrogen of the blood, and other manifestations of shock. That the fall in blood pressure is due to peripheral circulatory failure is indicated by the collapsed state of the superficial veins At the height of an Addisonian crisis, the

blood pressure in the antecubital veins may be so low that it cannot be measured by the direct method. On the other hand, in a patient with low arterial pressure who was feeling comparatively well in a remission, the venous pressure was normal. This would indicate that factors other than diminished venous return to the heart participate in the continuous hypotension of Addison's disease.

Observations by Swingle and Pfiffner[115] show that the decreased venous return to the heart and consequent shock which characterize the crises of Addison's disease are due to diminution in circulating blood volume. These investigators showed that in dogs the circulating blood volume falls following suprarenalectomy, and that when this diminution in circulating blood volume becomes sufficiently pronounced the arterial pressure drops and symptoms of shock appear. If a potent cortical extract or desoxycorticosterone acetate is then administered, the circulating blood volume rises and with it the arterial tension returns to normal and the symptoms of shock clear up. Swingle and Pfiffner showed that the non-protein nitrogen of the blood varies inversely as the arterial pressure. The rise in non-protein nitrogen during suprarenal shock would appear to the writer as most probably due to the cutting down of the blood flow through the kidneys as a result of the diminution in circulating blood volume and consequently cardiac output (page 623). Swingle and Pfiffner showed that the diminution in volume of circulating blood during suprarenal insufficiency is due to loss of plasma water, for both the red cells and the plasma proteins are increased in concentration. Losses of 40 to 50 per cent of the plasma were frequent in their experiments.

The next problem that arises is that of how deficiency of the suprarenal cortical hormone produces the decrease in the volume of circulating blood that in turn entails suprarenal shock. Swingle and Pfiffner established that in suprarenal shock administration of fluid does not dilute the blood stream and thus increase the circulating blood volume to the same extent as in normal controls. On the other hand, the injection of cortical extract promptly raises the blood volume and cures the symptoms of shock. On the basis of these findings, Swingle and Pfiffner concluded that the hormone of the suprarenal cortex regulates the blood volume through action on the fluid exchange between the capillaries and the tissue spaces and that with a deficiency of this hormone fluid is displaced from the blood stream to the tissue spaces with resulting drop in circulating blood volume and shock. But Harrop[68] and his associates found that in experimental suprarenal shock the tissues are dehydrated and the body weight falls, which shows that the loss of plasma water is not into the tissues.

New light has been thrown on the mechanism of the oligemia of suprarenal shock by recent investigations, notably those of Loeb[77]

and his associates, which indicate that the decrease in circulating blood volume may be secondary to loss of sodium. Marine and Baumann[78] found that following suprarenalectomy in cats the sodium content of the blood is lowered, and that the lives of the animals are prolonged by the administration of sodium chloride; that the chloride concentration in the blood is depressed in suprarenal insufficiency had previously been known. Rogoff[101] found the administration of sodium chloride an additional help in treatment of Addison's disease with cortical extract. Loeb and his associates showed that the sodium content of the blood is depressed in Addison's disease and that remarkable improvement can often be produced by the administration of sodium chloride without cortical extract. Also, the sodium content of the blood rises when cortical extract is administered to the adrenalectomized animal or in human Addison's disease. Loeb and his associates found that the sodium depletion in Addison's disease is caused by increased excretion of sodium in the urine Their conception is that the suprarenal gland regulates the sodium content of the blood through action on the kidney However, recent observations by Allers, Kendall, Wilder[1] and his associates, and others indicate that the loss of sodium in suprarenal insufficiency may be at least partly effected through the intermediacy of alterations in potassium metabolism During crises of suprarenal insufficiency, the potassium content of the blood is elevated and these investigators have found that the loss of sodium may be minimized by a low intake of potassium and aggravated by ingestion of large amounts of potassium. But whatever the mechanism of the loss of sodium, Loeb and his co-workers have found that the decreased sodium content of the blood results in diminution in the total base and that this is accompanied by decrease in the total acid of the blood. There is thus a diminution in the total electrolyte content of the blood. That this entails fall in circulating blood volume, consequent decrease in the venous return to the heart, and symptoms of shock has already been recalled

ACUTE DIFFUSE PERITONITIS

Acute and widespread inflammation of the peritoneum, contrary to that of the pleura, often produces peripheral circulatory failure and shock. The familiar peritoneal facies is that of shock. However, acute diffuse peritonitis does not always result quickly in shock; not rarely, on opening the abdomen for appendicitis, one finds widespread peritonitis although there has been no evidence of peripheral circulatory failure

That the circulatory failure resulting from peritonitis is of peripheral origin and not due to heart failure was shown by Heinecke[59] by animal experiments similar to those of Romberg and Paessler

(page 659). Clinically, this is evident from the collapsed veins, low venous pressure, and other symptoms and signs of shock. Olivecrona[88] found in experimental peritonitis that the circulating blood volume is diminished, which would seem to be an important factor in the pathogenesis of the decreased venous return to the heart Stagnation of blood in dilated capillaries in the enormous peritoneal surface may well play an important part in decreasing the volume of blood in active circulation. Extravasation of plasma into the peritoneal cavity may also be significant. Blalock[12] found that by manipulating the exposed intestines he could cause extravasation of sufficient plasma to produce shock through diminution in circulating blood volume. In acute peritonitis, respiration is purely thoracic and superficial, which diminishes the respiratory aid to the venous return to the heart. All of these factors may be summated in the production of peripheral circulatory failure in peritonitis.

PERIPHERAL CIRCULATORY FAILURE DUE TO BURNS

Typical peripheral circulatory failure with the clinical picture of shock is the most important and common constitutional manifestation of severe burns Such shock is much more apt to follow extensive though superficial burns than far deeper burns involving only a small area of the skin. If over two-thirds of the body surface is implicated in even a rather superficial burn, fatal shock generally ensues. On the other hand, the soft parts of a leg or arm may be charred with but little constitutional reaction.

The cause of shock in superficial burns has naturally excited much interest, and many theories have been proposed. (See Bardeen[8] for the older views) It now appears quite definite that the immediate cause of the peripheral circulatory failure is concentration of the blood with decrease in circulating blood volume and consequent fall in cardiac output. The diminution in circulating plasma volume which concentrates the red cells is of a degree scarcely paralleled in any other condition In one of Underhill's[117] cases, the hemoglobin content of the blood attained the almost incredible value of 230%, and in other instances it was almost as high. The concentration of the blood is so great that it becomes syrupy; thromboses often result. The combination of decrease in circulating blood volume and increase in viscosity of the blood offers an excellent explanation of the decrease in the venous return to the heart which causes the shock. (In an instance of ultimately fatal shock from a burn, I found the venous pressure under 1 cm. of water.) For a time the arterial pressure may be maintained by vasoconstriction despite the great concentration of the blood (well exemplified in some of Underhill's cases), but unless there is improvement the arterial tension falls sooner or later.

The studies of Underhill, Kapsinow and Fisk[118] and of Blalock[13] indicate that the fall in circulating plasma volume is accounted for by local exudation in the burned area in the form of weeping from the burn and of edema and blisters. The former investigators found in experimental burns that the local loss of fluid may amount to as much as 70 per cent of the blood volume. Moreover, the protein content of the extravasated fluid indicates that almost unchanged plasma is lost through the damaged capillaries in the burned area. The fact that shock in burns is due to local loss of plasma explains the above-mentioned observation that extensive superficial burns are so much more dangerous than circumscribed deep ones.

II. PERIPHERAL CIRCULATORY FAILURE AND SHOCK DUE TO MOTOR DYSFUNCTION OF THE VESSELS

The mechanism of this form of peripheral circulatory failure has already been discussed (page 618). Formerly, most instances of peripheral circulatory failure were regarded as induced by relaxation of the small vessels, especially the arterioles, and the condition spoken of as "vasomotor paralysis." However, we have just seen most of the common forms of peripheral circulatory failure appear to be due to oligemia rather than to motor dysfunction of the vessels But there appear to be a few forms of shock in which the motor dysfunction of the vessels seems to operate.

Primary Traumatic Shock.—Shock sometimes comes on almost immediately after causative trauma. Most often, this is due to profuse hemorrhage; such cases are considered in connection with hemorrhagic shock. In other instances primary shock (page 626) occurs in the absence of hemorrhage Classical examples are seen following the perforation of a peptic ulcer, in which the victim sometimes drops in his tracks and when seen by the ambulance surgeon a few minutes later may be pulseless. Violent blows on the abdomen ("solar plexus punch") or testicle may cause primary shock, and it also occurs in very severe wounds of any description without significant hemorrhage.

The very rapidity with which the symptoms of primary shock develop speaks strongly for their nervous origin, for which reason the condition has been termed *neurogenic shock*. Experimental support for this view was long ago afforded by the well-known "Klopfversuch" of Goltz.[49] He found that if a frog is tapped repeatedly on the abdomen the tone of the abdominal vessels is lowered to such an extent that most of the blood accumulates within them, the venous return to the heart diminishes, and the cardiac

output drops correspondingly. It seems a reasonable assumption that a similar nervous mechanism operates in primary traumatic shock in man However, it is no more than an assumption; the subject has hardly been susceptible to direct investigation because the patients usually succumb to or recover from primary shock very rapidly.

Spinal Anesthesia.—The shock which occasionally results from spinal anesthesia is doubtless due to similar relaxation of small blood vessels. Blalock and Bradburn[16] were able to produce the same type of peripheral circulatory failure by injury to the spinal cord. In experiments with spinal anesthesia, Burch and Harrison[20] found that the arterial pressure fell first and only later was the cardiac output diminished. Burch and Harrison interpreted this sequence as indicating vasodilatation with pooling of blood in the anesthetized areas and substantiated this inference by perfusion experiments which showed that the small vessels were actually relaxed.

In the past it has been generally assumed that the fall in blood pressure and shock in such conditions as primary traumatic shock and spinal anesthesia are due to relaxation of the arterioles. However, recent observations indicate that this conception may need modification. The observations of Smith, Goldring[108] and their associates point to the absence of important tonic activity in the vasomotor paths to most of the arterioles in the resting, recumbent individual. They found that when the blood pressure falls as a result of spinal anesthesia, the systolic falls more than the diastolic, which is the reverse of what would be expected from arteriolar dilatation. Smith and his co-workers interpret their findings to indicate that the decreased cardiac output in spinal anesthesia is due to relaxation of the postarteriolar stream bed (capillaries, venules, veins). Similarly, Weiss[120] and his collaborators found that the circulatory collapse which they induced by the administration of sodium nitrite to subjects in the upright posture is due to loss of tone of the veins with pooling of blood in these vessels.

Acute Pancreatic Necrosis.—Shock is an integral part of the clinical picture of acute pancreatic necrosis, having been present in over 90 per cent of Finney's[35] cases Pancreatic shock often evolves with remarkable celerity, and may be pronounced when a patient is seen within a few minutes after the onset of the agonizing epigastric pain. In those rare instances of sudden death in which acute pancreatic necrosis is found at necropsy, peripheral circulatory failure is doubtless responsible.

The peripheral circulatory failure is classical. The skin is pale and moist, the arterial pressure low, the veins collapsed, and the extremities cold not only during the initial period of normal or subnormal rectal temperature, but also after fever has set in. At first,

the pulse may not be rapid but it later accelerates. A remarkable feature in some instances is the appearance of bluish-red mottling of the skin, especially of the abdomen and arms Such *cutis marmorata* was more pronounced in a patient with acute pancreatitis than in any other instance of shock that I have observed. Diffuse cyanosis has also been described by Halstead[56] and others. The sensorium generally remains clear until close to the end.

The sudden onset of pancreatic shock makes it seem likely that it is one of the motor forms of shock. However, this has not been proved, and the actual pathogenesis is entirely obscure. Why peripheral circulatory failure should develop with such remarkable rapidity and constancy in acute pancreatic necrosis has not been elucidated. Although the pain in acute pancreatic necrosis is excruciating, this can scarcely be the sole cause of the shock; the most violent renal colic is sometimes accompanied by rise in blood pressure Pressure on the solar plexus by the swollen pancreas and liberation of histamine-like bodies from the necrotic tissue have also been incriminated (Archibald and Kaufmann[2]), but these are merely hypotheses.

III. CARDIAC SHOCK

The clinician uses the term shock to designate a symptom complex including weakness, pallor, profuse sweating, cold extremities, and feeble pulse. We have seen that this aggregate of symptoms manifests a quantitatively inadequate systemic blood flow produced by deficient cardiac output and widespread peripheral vasoconstriction resulting, probably reflexly, from the small cardiac output Most often the drop in cardiac output which causes shock is due to decrease in blood volume or motor dysfunction of the small vessels which diminish the venous return to the heart However, precisely the same clinical picture of shock may also result from fall in cardiac output due to primary heart failure of acute onset or intensification. The resemblance is so close that, to illustrate, in patients presenting the clinical picture of shock and complaining of epigastric pain, one is not uncommonly in doubt whether the situation results from coronary thrombosis with heart failure or an abdominal disorder with peripheral circulatory failure.

Since the symptoms of shock are the result of inadequate cardiac output, at first thought it seems paradoxical that they are more often due to peripheral circulatory failure than to primary cardiac insufficiency. As already intimated, the explanation is probably along the following lines:

In peripheral circulatory failure the venous return to the heart is diminished Since the heart acts as a force pump, and not as a

suction pump, it cannot "compensate" for this fall, and the cardiac output suffers an equal decrement. The only compensatory mechanism that comes into action is peripheral vasoconstriction. While this vasoconstriction tends to keep up the arterial pressure and maintain the blood flow to the central nervous system and heart, it augments the peripheral ischemia with its resultant anoxemia and thus participates in the production of some of the symptoms of shock (*e. g.*, the cold extremities and the acidosis).

In heart failure of other than acute inception, the situation is different. As has been seen in detail in Chapter XVIII and on page 45, the failing heart has compensatory mechanisms which tend to maintain the cardiac output. Take for example failure of the left ventricle in hypertension. When the left ventricle fails, systolic emptying is no longer as complete as before. The result is rise in the diastolic pressure in the left ventricle and accumulation of blood (engorgement) in the lesser circulation. The rise in pressure in the pulmonary veins augments the diastolic filling of the left ventricle, which in turn, in accord with Starling's law of the heart, increases the systolic accomplishment of the left ventricle. The high pressure in the engorged pulmonary veins thus tends to maintain the cardiac output at a higher level than would otherwise be the case. Moreover, the development of pulmonary engorgement is accompanied by increase in the total circulating blood volume (page 72). The result is that the individual with a gradually failing left ventricle, despite the accumulation of a large volume of blood in the pulmonary circuit, does not suffer from inadequate filling of other portions of the circulation. What thus happens in left ventricular failure of gradual onset is that decrease in cardiac output is avoided to a considerable extent at the expense of pulmonary engorgement.

According to this conception, augmented blood volume plays a fundamental part in maintaining cardiac output in chronic heart failure. However, the production of an increment in blood volume more substantial than that available immediately in the reservoirs is a process that takes some time. The result is that if severe heart failure sets in abruptly, as in coronary thrombosis, there is not enough time for the blood volume to rise, the compensatory mechanisms depending on the increase in blood volume do not function, the cardiac output falls, and the clinical picture is that of shock. Then, as the blood volume gradually rises, the manifestations of shock clear up, though those of pulmonary engorgement may become more intense; presumably, the rise in blood volume has facilitated the compensatory mechanisms described above which augment cardiac output. This sequence of events, though not correctly interpreted at the time, was illustrated in some studies on the circulatory

dynamics of myocardial infarction: "In initial attacks of myocardial infarction, in which the clinical picture is predominantly that of shock, the blood volume is subnormal or at the lower limit of the normal range. As the patient recovers from the shock, the volume rises. This was well illustrated in Case 14. When the patient first entered the hospital in typical shock due to myocardial infarction, the volume of circulating blood was only 49 cc. per kilogram, ten days later, when the manifestations of shock had largely cleared up, the volume of circulating blood had risen to 73 cc." (Fishberg, Hitzig and King[38]).

Considered from the point of view of pathogenesis, the symptoms of heart failure belong in two categories (1) Those due to engorgement of the circulation upstream to the failing chamber—the backward failure of Harrison (page 29); (2) those due to deficient blood flow resulting primarily from inadequate cardiac output and secondarily from compensatory peripheral vasoconstriction—the forward failure of Harrison When the heart failure is of acute onset, forward failure and the resultant clinical picture of cardiac shock tend to predominate; when the cardiac insufficiency is of insidious origin and chronic course, backward failure and the consequences of passive engorgement are dominant

Occurrence of Cardiac Shock.—Cardiac shock may be produced by any of the forms of heart failure, provided that the onset or intensification is sufficiently abrupt. The chief circumstances in which this occurs are the following.

1. Acute left-sided failure: The outstanding example is myocardial infarction (page 453). In individuals with coronary sclerosis, such manifestations of shock as sudden weakness, pallor, and sweating may be the only indications of myocardial infarction. In all forms of left ventricular strain, but especially in hypertension, sudden failure of the left ventricle may produce the picture of cardiac shock, which is often associated with acute pulmonary edema. The rare instances of obstruction of the stenotic mitral valve by a ball valve thrombus constitute classical examples of cardiac shock. The same is true of rupture of an aortic cusp, a papillary muscle, or one of the chordæ tendinæ.

2. Acute right-sided failure: Cardiac shock in typical form dominates the picture of acute *cor pulmonale* due to pulmonary embolism (page 553).

3 Acute generalized cardiac failure· The onset of auricular fibrillation or another disturbance in rhythm may produce shock. I have several times known such cases (in which there may be cardiac pain presumably due to coronary insufficiency) to be mistaken for coronary thrombosis. The myocarditis of diphtheria may also produce cardiac shock.

4. Acute hypodiastolic failure: Quickly developing tamponade of the heart due to pericardial effusion, especially purulent pericarditis or hemopericardium, may be manifested by cardiac shock.

Clinical Picture.—Detailed description of the symptomatology of cardiac shock at this point is unnecessary. The symptomatology is much the same as that of shock due to peripheral circulatory failure, which has already been depicted (page 620). The mark through which cardiac shock is often, though not always, differentiated from the shock of peripheral circulatory failure is by the coexistence of signs of pulmonary or systemic venous congestion. Thus, in myocardial infarction the pallor, sweating, feeble pulse and other manifestations of shock are often accompanied by evidences of pulmonary congestion or combined pulmonary and systemic venous engorgement; in pulmonary embolism, the shock is accompanied by swelling of the liver and neck veins and other consequences of severe right heart failure.

Symmetrical Peripheral Gangrene.—One very rare but interesting manifestation of shock may be described here because the best examples of the phenomenon that I have observed have been in cardiac shock, namely, symmetrical peripheral gangrene

It has long been known that obstruction of the mitral valve by a ball valve thrombus in mitral stenosis leads to intense coldness and pallor followed by deep cyanosis of the fingers, toes and frequently the tip of the nose and the ears, the process may go on to gangrene The picture is so typical that it may lead to suspicion of the diagnosis I have also observed the development of such symmetrical gangrene in very tight mitral stenosis without impaction of a ball valve thrombus and in myocardial infarction In each instance, the development of the peripheral gangrene accompanied the typical picture of cardiac shock. Postmortem examination revealed that the peripheral gangrene—as might have been surmised from its symmetry—was not due to embolization; this has been confirmed by Perry and Davie.[91] A clue to the pathogenesis of the gangrene was afforded by the observation[37] that while the veins of the neck were intensely engorged and bulging, those of the upper extremities were hardly visible In one of the cases it was impossible to insert a needle into an antecubital vein; in order to do so it was necessary to cut down, and direct observation revealed that the vein was almost empty and apparently contracted When a needle attached to a right-angled glass tube (page 113) was inserted into the bulging cervical veins the blood rose over 20 cm., while when it was put into the antecubital vein the blood hardly rose at all.

From these observations it would seem that what has happened is the following: The extreme diminution in cardiac output has led to powerful peripheral vasoconstriction The latter tends to maintain the arterial pressure and divert blood to the brain and heart, but at the same time produces so severe an ischemia of the extremities as to lead to gangrene The symmetrical gangrene of general circulatory failure is thus angiospastic in origin and the unfortunate side effect of a compensatory mechanism Incidentally, lesser degrees of the same phenomenon are often revealed in patients with severe right heart failure by much greater engorgement of the cervical than of the peripheral veins.

IV. CIRCULATORY FAILURE AND SHOCK IN THE FEBRILE INFECTIONS

Circulatory failure is an omnipresent danger in the severe acute infections. In two of the infections, rheumatic fever and diphtheria, heart failure is the outstanding form of circulatory insufficiency, and they have therefore been considered in preceding chapters. In most of the other common infectious diseases, however, peripheral circulatory failure is more common, although there may also be cardiac insufficiency. Before discussing the individual conditions, a few remarks on the circulation in fever may be in place.

The Circulation in Fever.—As might be anticipated, the circulation is profoundly affected in febrile states. Du Bois[30] found that in the infectious fevers—with the exception of tuberculosis, in which the increment in metabolism is rather less—heat production (basal metabolism) rises about 7.2 per cent for each degree Fahrenheit above the normal. This increment in oxygen consumption can be covered either by increase in the minute volume of the heart or by the utilization of a higher proportion of the arterial blood on each circuit through the capillaries. The meager evidence available indicates that both mechanisms may be called into play. In four subjects in whom fever was induced for therapeutic purposes by inoculation with the organism of relapsing fever, Bjerloew and Liljestrand[11] found that the *minute volume of the heart* rose proportionately to the oxygen consumption; the oxygen utilization did not change. Grollman[51] studied the effect of the injection of typhoid vaccine on the cardiac output His observations indicated that during the period when the fever was first rising, the increased oxygen consumption was covered entirely by increase in cardiac output. Later, though the fever rose still higher, the cardiac output fell and the increased oxygen consumption was mediated largely through increase in the arteriovenous oxygen difference In pyrexia induced by short-wave radiation, Kissin and Bierman[67] found that the velocity of blood flow is greatly increased, in one instance to more than 400 per cent of the normal value. The augmented cardiac output indicated by their findings would seem ample to cover the oxygen consumption without invoking increased arteriovenous oxygen difference; indeed, the blood flows so rapidly that the latter may well be sometimes decreased, though I am not aware that this has actually been demonstrated.

Vascular dilatation in inflamed areas—when these are extensive, as the intestine in typhoid fever—may be a factor of importance in inducing increase in cardiac output, at least to the extent that there is not counteracting vasoconstriction elsewhere. The play of the cutaneous vessels, so important in the regulation of temperature

and the pathogenesis of fever, is doubtless of significance in determining the cardiac output in fever; the superficial vasodilatation so common when the temperature is rising would favor increase in cardiac output, and constriction of the cutaneous vessels the reverse. Unfortunately, little positive information is available, largely because of the few determinations of cardiac output that have been carried out in fever.

Rise in temperature accelerates the *heart rate*. In 500 observations of pyrexia produced by short-wave radiation, Bierman and E. H. Fishberg[10] found that the heart rate increased an average of 8.5 beats per minute for each degree Fahrenheit of temperature elevation Similarly, Bazett[9] found that in pyrexia induced by external heat, the heart rate is accelerated by 8 to 10 beats per minute for each degree Fahrenheit above the normal. According to experimental data obtained by Bazett, the pulse rate is relatively faster when the temperature is rising than when it is falling. The electrocardiogram shows that the increased heart rate is a sinus tachycardia. It is partly due to the direct effect of the high temperature on the heart, for the excised heart is accelerated by warming. Presumably, the increased venous return due to the vasodilatation also reflexly accelerates the heart. However, the tachycardia of febrile diseases cannot be wholly a consequence of the elevation of temperature, for it varies with the nature of the sickness, *e. g.*, the relatively slow pulse of typhoid fever. It seems evident that other, as yet obscure factors enter. With the onset of circulatory failure, the pulse generally becomes accelerated out of proportion to the temperature.

In pyrexia produced by short-wave radiation, Bierman and E. H. Fishberg found that the *systolic pressure* usually shows a slight elevation followed by a gradual fall to a point below the original level. The *diastolic pressure* at first falls, but after an hour or two rises until it reaches a point slightly above the original value; these findings would indicate initial vasodilatation followed by vasoconstriction. In the acute fevers of human disease, the arterial pressure is often little affected, but may vary in either direction. Sometimes there is depression of both systolic and diastolic pressures, which is inconsiderable in the absence of circulatory failure. The drop in arterial tension is probably due to peripheral vasodilatation. On the other hand, Robertson and Bock[11] and Bazett have described cases of wound infection during the World War in which the systolic pressure rose as high as 150 mm. for days. Bazett interprets such a rise in pressure as a manifestation of widespread vasoconstriction which serves to force more blood through the dilated vessels of the infected area. I have repeatedly seen similar rises in systolic pressure at the onset of "sthenic" cases of pneumonia, puerperal sepsis, and other acute

fevers (page 665). In these cases, the pulse is apt to be bounding and the pulse pressure increased; the presence of capillary pulsation may indicate the peripheral vasodilatation.

Opposing influences act on the *circulating blood volume* in fever In at least many forms of pyrexia there is an increased loss of water from the skin and lungs which tends to decrease the plasma volume unless replaced by augmented fluid intake. On the other hand, Barcroft (page 61) found that elevation of environmental temperature tends to increase the blood volume by mobilization of red cells from the reservoirs; it is to be presumed that the same tendency results from elevation of body temperature in fever. Gibson and Kopp[48] have made careful observations of the blood volume in artificial fever. In fever produced by the injection of typhoid vaccine they found little change in plasma volume but a slight increase in total blood volume due to influx of erythrocytes. But when Gibson and Kopp produced fever by the Kettering hypertherm or diathermy, there was a marked reduction in plasma volume which was only partially offset by mobilization of red cells so that the total circulating blood volume declined in the large majority of patients. Unfortunately, only fragmentary data are available regarding blood volume in the fever of disease Eppinger and Schuermeyer[32] observed that in a malarial paroxysm with temperature of 40.5° C., the circulating blood volume rose from 3420 to 3930 cc Wollheim[122] found the circulating blood volume increased in fever In scarlet fever, typhoid fever, and erysipelas without evident circulatory failure, Grunke[53] detected no constant change in the circulating blood volume; in some cases, it was increased, but in very severe typhoid or scarlet fever, it was diminished. Because of the rôle of oligemia in the pathogenesis of shock, it seems important to collect more data on the blood volume in severe infections

Types of Circulatory Failure in the Acute Infections.—Until the end of the nineteenth century, circulatory collapse in the acute infections was all but universally attributed to cardiac weakness. Laennec[70] had observed that the heart sounds often become feeble at the height of the infectious fevers. This observation was confirmed by Stokes[111] who also furnished, especially on the basis of his observations in typhus fever, a classical description of the rapid and often irregular heart action, fetal heart sounds, impalpable apex impulse, feeble radial pulse, pallor on sitting up, and other phenomena of circulatory collapse in the acute infectious diseases He attributed the circulatory collapse to heart failure. This conception remained dominant until the work of Romberg[102] and his associates at the end of the last century. These investigators inoculated animals with pneumococci, diphtheria, and pyocyaneus bacilli. At the height of the infection, the animals developed circulatory collapse similar to that occurring in human infectious

diseases. Romberg and his co-workers were able to show that the circulatory collapse was not due to cardiac weakness. For when they compressed the aorta, or increased the venous return to the heart by means of appropriate abdominal massage, the arterial pressure rose quite as much as in normal controls—a demonstration that the heart was still functionally competent and not responsible for the circulatory failure.

In other instances, the symptoms of the circulatory insufficiency are clearly those of heart failure. In the acute infections, therefore, two primary varieties of circulatory failure are to be differentiated, *viz.*, heart failure and peripheral circulatory failure.

Heart Failure in the Acute Infections.—It has generally been assumed, without direct proof, that heart failure in the infections results from myocardial damage due to toxic products. A contributory factor may also be the increased work of the heart necessitated by the elevation of temperature (page 657). In pneumonia there is also the effect of anoxemia and the increased resistance which the right ventricle must overcome; a similar factor operates in whooping cough.

Electrocardiographic studies have shown that myocardial damage is more common in the acute infections than was previously appreciated. Nevertheless, apart from the two outstanding exceptions of rheumatic fever and diphtheria, it is to be emphasized that circulatory failure in the acute infections is much more often of peripheral than of cardiac origin. Most instances of definite and severe heart failure that I have observed to develop in the course of acute infections have been elderly individuals, and in a high proportion there was good reason to believe that there was arteriosclerotic or other disease of the heart prior to the onset of the infection. *The previously healthy heart rarely gives way during an acute infectious disease* other than rheumatic fever or diphtheria.

The clinical picture of cardiac failure in the acute infections is the conventional one of insufficiency of the left and right sides of the heart; either may predominate. Most often, the picture is complicated by evidences of peripheral circulatory failure. Respiration is accelerated out of proportion to the fever, and there may be dyspnea. Cardiac pain and substernal oppression are rather rare complaints; palpitation is much more common. Cyanosis may be present, but is usually of a grayish hue because of simultaneous peripheral circulatory failure. Swelling of the superficial veins and liver may testify to the insufficiency of the right heart. Unless brought on by large infusions, pitting edema is very rare, possibly largely because fever militates against water retention and the duration is usually but short. The apex beat, if previously strong, becomes weak, more diffuse or impalpable. The pulse is rapid, small, in severe cases "thready," and perhaps irregular.

Enlargement of the heart to the right or left may be demonstrable by percussion or displacement of the apex beat, but one must guard against deception by upward displacement of the diaphragm due to meteorism, which is much more common than cardiac enlargement sufficient to be demonstrable by percussion. Apart from cases with heart block, rare except in diphtheria, the heart rate is accelerated over its previous *tempo;* premature contractions, auricular fibrillation, or other arrhythmias may develop, but are usually transitory and fluctuate rapidly. It is to be emphasized that distant heart sounds, fetal heart sounds, feeble pulse, and rapid cardiac rate are not necessarily evidences of myocardial damage, but may, and most often do, result from peripheral circulatory failure. Murmurs due to relative insufficiency of the auriculoventricular orifices may develop, but, because of the great frequency of systolic murmurs, can be suspected as such only when other evidences of heart failure develop coincidently. Gallop rhythm, when present, affords an unequivocal sign of heart failure, and should be carefully sought for in every acute infection. The arterial pressure is generally depressed, but, other than terminally, is not affected as much by heart failure as by peripheral circulatory failure The electrocardiogram often affords evidences of myocardial damage in infectious disease where symptoms or physical signs of heart failure are not evident.

Peripheral Circulatory Failure in the Acute Infections.—Except in rheumatic fever and probably diphtheria, circulatory failure in the acute infectious diseases is far more often of peripheral than of cardiac origin. The clinical picture is fundamentally the same as that of traumatic shock, and differs only in those details which are due to the terrain of the infectious disease in which it occurs. The skin is pale and sweating, such cyanosis as develops is grayish and subordinated by the pallor, there may be cutis marmorata, and the extremities and nose are cold. While the breathing may be rapid, there is little or no dyspnea and no orthopnea. The pulse is feeble, thready, usually rapid, and previous dicrotism may disappear. The superficial veins are collapsed and the venous pressure is low. This symptomatology, especially the state of the veins, leaves no doubt that the patient is suffering from peripheral circulatory failure, and not from cardiac insufficiency, a differentiation of the greatest practical importance.

Much remains to be learned concerning the pathogenesis of peripheral circulatory failure in the acute infections. As a result of the above-mentioned investigations of Romberg and his associates, they concluded that the circulatory failure was due to injury to the vasomotor center by toxins. This conclusion was based on their finding in animals in circulatory collapse following infection with pneumococci, pyocyaneus, or diphtheria bacilli, that (1) the

heart was functionally competent (page 659) and (2) the reflex rise in blood pressure which normally follows stimulation of certain sensory nerves did not occur. They concluded that these findings indicated a depression in the irritability of the vasomotor center. This conclusion was accepted for some years, but subsequent work has shown it to be unfounded. The experimental work cited on page 628, which demonstrated that in traumatic shock the peripheral arterioles are not only not relaxed but actually constricted would seem to hold equally well for peripheral circulatory failure of infectious origin. Further, Porter and Pratt[90] showed that the vasomotor center is especially resistant to damage resulting from infections with the diphtheria bacillus and the pneumococcus. Even when the animals were in severe circulatory failure, if the blood pressure was elevated by saline infusions, the function of the vasomotor center promptly improved, indicating that any diminution in irritability was a consequence of the low blood pressure and not a cause of it. In later experiments, Porter and Newburgh[91] produced pneumonia in dogs, cats, and rabbits. They judged the condition of the vasomotor center from the reflex change in blood pressure resulting from stimulation of the depressor, the sciatic, and the central end of the vagus nerves, and found that it was normal. At present, therefore, there would seem to be little, if any, evidence that circulatory collapse and fall in blood pressure in infectious diseases is due to damage to the vasomotor center.

The close similarity between the symptomatology of circulatory collapse in the infections and of traumatic shock suggests strongly that the former is also due to diminution in circulating blood volume. Unfortunately, however, this is as yet but a theory, for there have been, so far as I am aware, no systematic studies of the circulating blood volume in circulatory collapse resulting from infections Grunke[92] found that the circulating blood volume is almost always diminished in severe typhoid and scarlet fever, but his patients had *no* circulatory failure. In experimental peritonitis, Olivecrona[93] found that circulatory failure follows fall in circulating blood volume If circulatory collapse in the acute infections is actually mediated by decrease in circulating blood volume, the mechanism of the latter remains to be elucidated. An important factor in many instances is doubtless excessive loss of water and salts through the skin and lungs which is not replaced because of anorexia, vomiting or diarrhea. In keeping with an important rôle of this factor is the observation of Gibson and Kopp[94] in artificial fever that loss of water at a rate exceeding 5 cc. per hour per kg. body weight involved serious risk of peripheral circulatory failure Edmunds and Johnston[95] have published experiments indicating that peripheral circulatory failure in diphtheria is due to action of the toxin on the myoneural junction of the splanchnic nerves with result-

ant stagnation of blood in the relaxed splanchnic vessels and diminution in the venous return to the heart. It is conceivable, but not proved, that circulatory failure in some of the infections may be due to damage to the capillaries by toxic substances, with consequent stagnation of blood in the dilated vessels and extravasation of plasma. The entire field is obscure and in need of investigation.

PNEUMONIA

An omnipresent danger in pneumonia is circulatory failure. This may be of either peripheral or cardiac origin. It will be seen in the following that when the heart is healthy at the start of pneumonia, the danger of cardiac insufficiency is very remote and when circulatory failure develops it is almost always of peripheral genesis. On the other hand, in the common cases in which pneumonia develops in an individual with antecedent heart disease, cardiac failure is the chief danger.

The Work of the Heart in Pneumonia.—The heart is called upon to perform increased work in pneumonia In experimental pneumonia in dogs, Harrison and Blalock[65] found that the cardiac output is generally increased. Although determinations of cardiac output in pneumonia in man are not available, there seems good reason to believe that this circulatory variable is increased. The greater oxygen consumption entailed by the fever presumably necessitates augmentation of cardiac output to the extent that it is not covered by higher arteriovenous oxygen difference And inasmuch as the blood flowing through the consolidated lobes is defectively aerated, a useful purpose would be served by increasing flow, not only through the remainder of the lungs, but also through the systemic circuit, so that a greater volume of flow could counteract the decreased oxygen saturation of the arterial blood That such increase in blood flow through the intact lobes actually occurs is strongly indicated by Gross'[52] demonstration of great vascular dilatation in these parts of the lungs.

A second factor in increasing the work of the right ventricle is greater resistance in the pulmonary circuit. The presence of augmented pulmonary resistance and consequent hypertension in the pulmonary artery is revealed by the accentuation of the pulmonic second sound that is generally audible. The increased resistance to blood flow through the lungs seems to be largely the result of impermeability of the minute vessels in the consolidated areas Kline and Winternitz[68] showed, in both human and experimental pneumonia, that an injection mass penetrates but little into a consolidated lobe as a result of fibrin thrombi in the capillaries and even some of the larger vessels. Similarly, Gross[52] showed, by means of roentgenograms of pneumonic lungs previously injected

with a radio-opaque substance, that very little blood can flow through the consolidated lobe. It is this ischemia that accounts for the color of gray hepatization. As mentioned above, Gross showed that the decrease in the vascular bed of the consolidated lobes is to some extent compensated by vasodilatation in the other lobes. But with extensive consolidation this can scarcely be equal to the diminution in the vascular bed in the involved areas. The right ventricle is thus forced to pump an abnormally large minute volume through a narrower stream bed, with resultant increase in work.

Myocardial Damage in Pneumonia.—Not only is the work of the heart increased in pneumonia, but some have thought that the heart muscle often suffers significant functional impairment. Using careful roentgenological methods, Levy[73] found evidence of cardiac dilatation in 61.9 per cent of patients with lobar pneumonia. Stone[112] detected dilatation of the right ventricle in 39.4 per cent of 89 necropsies in lobar pneumonia and in 36 per cent of 112 necropsies in bronchopneumonia. However, slight or moderate dilatation can scarcely be considered good evidence of notable functional impairment of the heart; it may merely be part of the mechanism of adaptation to increased work of a heart still in good condition (page 298). Histologically, Stone observed parenchymatous, fatty or hyaline degeneration, or cellular infiltration, in 79.3 per cent of his necropsies. This finding likewise tells little regarding the functional capacity; similar observations can be made in almost any febrile disease whether or not heart failure is present. In experimental pneumonia, Newburgh and Porter[87] found no evidence of cardiac insufficiency; the heart of an animal dying of pneumonia contracted as well, when perfused with pneumonic blood, as that of a normal control.

Electrocardiographic Findings.—By making daily records, Master, Romanoff, and Jaffe[80] detected electrocardiographic changes in over 93 per cent of 45 patients with lobar pneumonia. Taking less frequent records, De Graff, Travell, and Yager[29] found electro-cardiographic abnormalities in about one-quarter of 975 cases. The changes were almost always transitory and included prolongation of the $P-R$ interval (complete block is a great rarity), abnormalities of the $R-T$ transition, flat, inverted, and large T waves, intraventricular block, and various arrhythmias. Master and his associates found changes in the $R-T$ interval simulating those seen in coronary artery disease to be the most common abnormality in the electrocardiogram. De Graff and his co-workers observed auricular fibrillation or flutter in 5 per cent of their patients, paroxysmal tachycardia less often. A remarkable feature of the electrocardiographic changes in pneumonia is that they are apt first to appear after the temperature has dropped to normal; this was true

in 78 per cent of the instances of prolonged auriculo-ventricular conduction time observed by De Graff *et al.* The electrocardiographic changes presumably bespeak myocardial damage of toxic origin. While anoxemia may also damage the heart muscle, it is hardly concerned when the changes first appear after defervescence Moreover, Master and his associates were unable to affect them by the administration of oxygen. The reason why electrocardiographic abnormalities often first appear after the fever has subsided is obscure. The prognostic significance of prolonged auriculo-ventricular conduction and changes in the $R-T$ interval does not appear to be great. On the other hand, the findings of the abovementioned investigators indicate that the mortality is higher in patients with auricular fibrillation or flutter or inversion of the T waves, although there are many recoveries in the presence of these findings.

Circulatory Measurements.—Most patients with pneumonia have *tachycardia.* De Graff and his associates found that the heart rate tends to remain fairly constant during the febrile period of the disease and that, as has long been known, very fast rates are associated with a poor prognosis. The outlook is gloomy when the ventricular rate exceeds 140 in an adult. De Graff's observations indicate that the later in the disease marked tachycardia develops, the worse the outlook. This is probably due to the tachycardia being an expression of severe toxemia, massive bacteriemia, peripheral circulatory failure, or such complications as endocarditis or pericarditis; in other words, the heart is rapid because the patient is doing poorly, rather than that the patient is sinking because his heart is rapid. It is interesting that De Graff observed heart rates of under 90 per minute in 11 3 per cent of his patients, including some with high fever. Marked *bradycardia,* even less than 50 per minute, is common during convalescence; the same is true of sinus arrhythmia.

The *arterial tension* often exhibits little change in the course of favorably progressing cases of lobar pneumonia, but the tendency is to elevation of pressure. In 17 such cases, Perry[89] found that the systolic pressure before the crisis averaged 128 1 mm, as contrasted with 117 9 mm when they left the hospital; the diastolic pressure was practically the same on both occasions. This slight rise in systolic tension is presumably attributable to increased cardiac output associated with fever. It was formerly widely held that the outlook is poor when the pulse rate exceeds the systolic pressure in adults (Gibson's rule), but this rule has many exceptions. Newburgh and Minot[86] found that the inversion is almost always due more to elevation in pulse rate than to fall in systolic pressure, and that even in fatal cases the arterial tension is often maintained until close to the end. In patients with pre-existing essential hyper-

tension, the blood pressure often, but *not always, falls sharply* during lobar pneumonia; the same is true in other febrile illnesses.

King, Hitzig, Bullowa, and the writer[66] found the *circulating blood volume, arm-to-tongue and arm-to-lung circulation times,* and *venous pressure* within normal limits in lobar pneumonia without circulatory failure

Heart Failure in Pneumonia.—In the foregoing, we have seen that the work of the whole heart, and more so of the right ventricle, is increased in pneumonia. This augmented work is performed by *a myocardium which is often damaged. Nevertheless, it is to be* emphasized that *heart failure is decidedly unusual in patients who enter lobar pneumonia with a healthy heart.* In 75 patients studied at the height of lobar pneumonia, Hitzig, King, Bullowa and the writer[66] found the arm-to-tongue circulation time prolonged above normal in only 8, of whom 4 had pre-existent heart disease. Even the cases with transitory auricular fibrillation or flutter most often do not exhibit the signs of heart failure in the form of passive congestion of the lungs or systemic veins. In the past, heart failure *was considered common, a conception which led to the* routine digitalization of patients with pneumonia. But with the clearer differentiation of peripheral circulatory failure, it became evident that peripheral and not cardiac mechanisms were responsible for the dreaded complex of cold extremities, grayish cyanosis, tachycardia disproportionate to the fever, and fall in blood pressure. In most of the instances of cardiac failure in pneumonia that I have seen, there was evidence of previous heart disease, or this was revealed at necropsy in the form of coronary arteriosclerosis. Brooks[18] *found that heart failure is the most common* cause of death when pneumonia develops in patients with antecedent cardiac disease—quite the reverse of what is seen when the heart was previously healthy.

When the heart fails in pneumonia, this is most often revealed by swelling of the systemic veins and rise in venous pressure. Right heart failure sufficiently pronounced to result in swelling of the liver or dependent edema is a great rarity apart from patients with evident pre-existing heart disease. Gallop rhythm may appear but is unusual. At least a large majority of instances of generalized pulmonary edema complicating lobar pneumonia are not due to heart failure. In 8 such cases, 7 of which were fatal, Hitzig, King, Bullowa and the writer[66] found the arm-to-tongue circulation time normal, which speaks strongly against passive congestion of the lungs due to heart failure. It is conceivable that the edema results from the concomitance of high pressure in the pulmonary circuit (page 663) and increased permeability of the capillaries due to anoxemia. That a tendency to transudation presumably due to

capillary damage often exists at the height of lobar pneumonia is indicated by the findings of Maver[81] and Schwartz and Harrison,[54] who demonstrated the presence of occult edema of the skin by means of the elastometer and the intracutaneous salt solution test

As would be anticipated, heart failure affects the prognosis in lobar pneumonia very unfavorably. Thus, Kastlin and Maclachlan[63] found that of 34 patients with pneumonia and elevated venous pressure, 24 died; while of 37 patients with normal venous pressure, only 5 succumbed. But even with very severe heart failure, there may be recovery.

Peripheral Circulatory Failure in Pneumonia.—Shock is one of the developments most to be feared in pneumonia. Except for patients with antecedent heart disease, whose greatest danger is heart failure (see above), death in pneumonia is generally ushered in by peripheral circulatory collapse. The picture is the classical one of shock: ashy pallor sets in, the cyanotic parts become grayish-blue, the features are sunken, the extremities and skin in general are cold in relation to the rectal temperature and covered by clammy perspiration, the previously bounding pulse becomes small and rapid out of proportion to the temperature, the peripheral veins are collapsed, and the venous pressure is low. While the arterial pressure sooner or later falls, unless recovery is rapid, it is surprising in some cases how long the arterial tension is maintained after other features of shock are pronounced. Kempmann[65] mentions cases in which the diastolic pressure falls very low with much less depression of the systolic tension, I have made the same observation . Peripheral circulatory failure in pneumonia is, of course, very menacing, but recovery from even severe collapse is not rare, especially when the latter occurs early in the disease.

Circulatory collapse may occur at any period of pneumonia, even after the crisis. Rarely, the onset of the disease is accompanied by circulatory collapse. It may appear with startling suddenness in a patient who seems to be running the conventional course of the disease, and cause death simulating that of pulmonary embolism. Both shock and heart failure may occur in the same patient.

Little is known concerning the cause or mechanism of peripheral circulatory failure in pneumonia Brooks[18] believes that sepsis is the most common basic factor in causing death in lobar pneumonia, and it may be that toxic damage to the capillaries is important in bringing about the circulatory failure Anoxemia may also injure the capillaries. In studies on the reactions of the small vessels of the skin to epinephrin and stroking, Perry[80] found evidences of impaired efficiency in the contractility of the capillaries at the height of lobar pneumonia. Other findings likewise indicating capillary damage in pneumonia are cited on page 666 Perry

believes that the impaired contractility of the capillaries is significant in the circulatory failure of pneumonia.

Whether decrease in circulating blood volume participates in the pathogenesis of peripheral circulatory failure in pneumonia remains to be determined, but to the writer seems *a priori* probable. In pneumonia without circulatory failure, the circulating blood volume is normal (King, Hitzig, Bullowa, and the writer[66]). But this tells nothing regarding the blood volume in cases with collapse. Sunderman, Austin and Camac[113] showed that the well-known hypochloremia of pneumonia is accompanied by decrease in the total base and electrolyte concentrations in the serum, and this may well constitute a factor predisposing to decrease in circulating blood volume (page 647). In some instances with extensive hepatization, the loss of plasma into the pneumonic lungs may constitute a serious drain on the blood volume. Studies on the blood volume during collapse are needed.

TYPHOID FEVER

After a protracted period of severe toxemia in typhoid fever evidences of circulatory failure may appear. These are especially apt to develop in older individuals after several weeks of severe illness, and are rare before the end of the second week. Most often the circulatory symptoms are commingled with more dramatic nervous and abdominal manifestations, so that they may escape detection by other than a careful examiner. From the literature it would appear that circulatory failure is much less common since patients with typhoid fever have been adequately nourished.

Because of the depressed sensorium of most of the patients, the first suspicion of circulatory failure is usually derived from the objective signs. Acceleration in pulse, fall in arterial pressure, and coldness of the extremities are the most common. Increase in pulse rate *pari passu* with decline in temperature has long been considered as a particularly ominous indication that the circulation is giving way, especially when, as is so often the case in typhoid fever, the pulse has been relatively slower than would correspond to the pyrexia. With the development of circulatory failure, dicrotism may diminish or disappear. The systolic murmur of relative mitral insufficiency may develop, and in severe cases embryocardia or gallop rhythm appears. Evidence of dilatation of the heart is hazardous to interpret because of the frequent displacement of the diaphragm, and with it the heart, by meteorism. With severe collapse, the patient becomes very pale and the lips and fingers may acquire a grayish cyanosis. Tachycardia and dyspnea are frequent, but may result from various causes in these severely ill patients. Evidences of right heart failure in the form of engorgement of the veins and liver and cardiac edema are rare. Hypostatic congestion

at the bases is common in long-standing cases, but generalized pulmonary edema is rare other than as a terminal manifestation; one must beware not to interpret bronchitic râles as evidences of pulmonary engorgement.

Often, circulatory failure is but a transient episode in the course of typhoid fever, detected only by the examination of the pulse, heart, and blood pressure, and passing away within a few days. In other cases, the circulatory collapse becomes more menacing, and is the chief cause of death in elderly individuals.

Pathogenesis.—Clinicians of the last century mostly attributed circulatory collapse in typhoid fever to damage to the heart muscle —typhoid myocarditis. This interpretation was largely based on the detection at necropsy of a flabby heart. Histologically, cloudy swelling, deposition of fat, increase in the pigment granules at the poles of the nuclei, vitreous change, and various other regressive changes are common, occasionally, in cases of some duration, interstitial infiltration is more or less prominent (Fiessinger and Rodowska[36]). In some cases, gallop rhythm reveals the cardiac weakness. More recent studies have shown that electrocardiographic evidences of myocardial damage are not rare. Thus Brow[19] found that in 14 of 65 cases of typhoid fever, the $P-R$ interval was prolonged to between 0 21 and 0 28 second, the prolongation of the conduction time generally developed in the second and third weeks and most often lasted two to four days. Rare instances of transitory complete heart block in typhoid fever have been observed

Despite these findings, circulatory disturbance in typhoid fever is rarely the result of cardiac weakness alone. The above-mentioned anatomical and electrocardiographic abnormalities are found with perhaps equal frequency in typhoid fever without circulatory failure other than terminal; and indeed the flabbiness of the heart muscle on which the older clinicians laid so much stress is probably only a sign of rapid postmortem decomposition The clinical picture in most cases also speaks unequivocally for the view that the circulatory failure is predominantly of peripheral and not of cardiac origin; the systemic veins are collapsed (venous pressure unmeasurably low in a recent case) and symptoms and signs of pulmonary engorgement, other than terminal pulmonary edema, are absent. Evidently, though the heart muscle is damaged, the peripheral circulatory failure in most cases decreases the venous return to the heart sufficiently for the weakened organ to master it and prevent the development of engorgement. Further, the possibility is to be borne in mind that some of the manifestations of cardiac weakness may result primarily from decreased coronary flow due primarily to the peripheral circulatory failure.

Another variety of circulatory disturbance is that developing after the fever has disappeared and convalescence is established

During this period, many patients present a striking lability of the pulse, which is readily influenced by exertion or excitement. In some instances, this lability is exaggerated, and the patients complain of palpitation and dyspnea on slight exertion. In such cases, the pulse rate may be 100 or more for weeks or even months after defervescence. Sooner or later, the symptoms clear up. Whether they are related to myocardial damage sustained during the febrile period or are of other origin remains to be determined. Whether typhoid fever leads to permanent cardiac damage also requires investigation. Thayer[116] found that systolic murmurs developing during the febrile period not rarely persist, and that 12 of 188 cases of typhoid fever followed for from three months to fourteen years after convalescence showed some indication of organic cardiac disease. Of those in whom an apical systolic murmur was detected during the attack, nearly one-quarter later exhibited evidences of organic damage to the heart.

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CHAPTER XXXIII

THE TREATMENT OF HEART FAILURE: I. GENERAL MEASURES

REST

REST is a cardinal therapeutic measure in heart failure, one which often suffices unaided to restore compensation. Some of the reasons for the value of physical and mental rest in heart failure are as follows:

1. Exertion involves increase in cardiac output and usually also in mean arterial pressure, as a result of which the work of the heart is increased. There is strong evidence (see Chapter XIX) that most instances of heart failure result from changes in the state of the heart muscle analogous to, if not identical with, what is known as fatigue in skeletal muscle. Avoidance of the increment in the work of the heart due to exercise or excitement tends to prevent such fatigue.

2. Exertion is accompanied by acceleration in rate with consequent shortening of the diastolic rest period. Abbreviation of the diastolic rest period is especially deleterious when the heart is hypertrophied or dilated; for with hypertrophy the diffusion of oxygen to the center of the fiber takes longer and with dilatation more oxygen is required for a given amount of work (Chapter XIX). Through slowing the heart and prolonging diastole, rest favors adequate metabolic exchange between the blood and muscle fibers and consequently tends to avert fatigue and failure.

3. Dilatation is part of the mechanism by which the heart accommodates itself to increased work. But with dilatation the efficiency of the heart muscle is decreased in the sense that more oxygen is consumed for a given amount of external work. Further loss of efficiency by the failing heart is obviously undesirable, and through averting such a decrement in efficiency due to the dilatation with increased work, rest combats fatigue and failure.

4. In left-sided failure, the increased venous return engendered by exercise augments pulmonary engorgement. The resulting dyspnea entails greater work of the respiratory muscles and thus further increases the work of the heart. Rest thus not only diminishes the work of the heart directly but also removes the secondary increment in cardiac work due to the pulmonary engorgement.

5. The requisite food and fluid intake is less at rest, which diminishes the work of the heart (page 681).

6. In individuals with hypertension, there is often a striking fall in blood pressure on rest, which spares the heart.

7. The symptoms of heart failure appear when the work of the heart approaches close to its maximal functional capacity. Rest thus tends to remove the dyspnea, edema, swelling of the liver, and other manifestations of cardiac insufficiency in proportion to the decrease in the work of the heart.

In the light of these facts, it is not surprising that heart failure often improves strikingly on bed rest alone. Many individuals with long-standing cardiac lesions learn this so well that when dyspnea, swelling of the feet, or other evidences of heart failure appear, they take to bed of their own volition. No great problem regarding the desirability of bed rest is usually presented by the patient with *initial* heart failure, the treatment of such an individual is best started with bed rest. In cases with severe heart failure, of course, there is no alternative, and the follow-up studies of Davis[7] indicate that longer periods of bed rest tend to be followed by more prolonged freedom from recurrence of heart failure. But even in mild failure, economic conditions permitting, it seems wise to the writer to initiate treatment by putting the patient to bed, even though for only a few days. The duration of the stay in bed is then decided in accord with the progress of the case.

The difficult problem is how to manage patients who, despite bed rest, appropriate diet, fluid restriction, digitalization, etc., remain with a limited cardiac reserve. In such cases, the clinician must be guided by the subjective sensations of the patient, none of the many "functional tests of the heart" are of assistance in practice. The general principle is that the patient must confine himself to such efforts as experience has shown him do not bring on dyspnea, palpitation, cardiac pain, weakness, or swelling of the feet. Unfortunately, this ideal cannot always be attained. It may not be possible for a salesgirl with mitral stenosis to give up her work even though she has swelling of the feet every evening which clears up during the night, or for a mother to stop looking after her household even though she must occasionally sit down to catch her breath. One is often astounded how many years individuals may carry on with a limited functional capacity of the heart. It is an important part of the physician's duty to advise such persons how to obtain the maximum rest while still continuing to carry out their duties. For instance, many an individual with a cardiac lesion who works all week will go to the beach on Sunday when he would be much better advised to rest at home. Especially important for cardiac patients, notably those with hypertensive and arteriosclerotic heart disease, is rest after meals. In addition to the functional capacity of the heart, the nature of the cardiac lesions is of significance when deciding upon the dura-

tion of bed rest. Individuals with rheumatic heart disease should remain in bed as long as there is evidence of activity of the rheumatic process, even though there are no symptoms of heart failure (page 767). The same is true following coronary thrombosis.

It should be remembered that when the patient is put to bed he should secure, as far as feasible, mental as well as physical rest. In fact, in individuals with hypertensive or arteriosclerotic heart disease, the mental rest may be more important than the physical. It should be remembered that if a business man is worrying about absence from his affairs, the "rest" may be doing him more harm than good.

While in bed, the cardiac patient should be propped up in the position in which he is most comfortable. Adequate sleep is an intrinsic part of rest and should be secured, although this is often difficult because insomnia is a common symptom of heart failure. Barbital derivatives or, if necessary, opiates may be used; morphine is often indispensable and sometimes initiates remarkable improvement. In cardiac psychoses, paraldehyde may be required.

Although rest is the prime therapeutic measure in heart failure, great harm can be wrought by prescribing it when there is a cardiac lesion but no heart failure. Many individuals with faultlessly compensated valvular lesions or hypertension, or with coronary arteriosclerosis, develop a superadded anxiety neurosis with fear of "dropping dead" and are afraid to take exercise. The management of such patients requires great tact on the part of the physician. He must convince the patient that not only is moderate exercise not harmful but actually beneficial. In many such cases, especially those with coronary sclerosis, the physician needs courage to prescribe exercise or insist that the patient leave bed or attend to business, for he will probably be blamed if an unpredictable catastrophe occurs. In recent years there has been too great a tendency to condemn to invalidism many individuals with heart affections, especially coronary disease, still capable of accomplishing much with little if any resultant shortening of life (*cf.* the splendid paper of White[30]). Particularly unfortunate has been the acceptance of electrocardiographic evidences of myocardial damage *per se* as obligate indications for retirement from affairs. The world would be much poorer if every individual who passed through coronary thrombosis or suffered from angina had hoisted the white flag; there have been many unsung John Hunters.

DIET

A fundamental principle in the treatment of heart failure and angina pectoris is to reduce as much as feasible the work of the heart. Appropriate dietetics often aids appreciably in this prin-

ciple of sparing the heart. Before discussing the composition of the diet in heart failure and angina pectoris, a few words regarding the relation of the food intake to the work of the heart may be useful.

Influence of the Dietary Régime on the Work of the Heart.—The ingestion of food increases the work of the heart. Gladstone[10] found that following a hearty meal the cardiac output is increased about 25 per cent; since the arterial pressure is usually a little elevated, the work of the heart is augmented even more. Moreover, not only is the work of the heart increased after a heavy meal, but it is also likely that the heart functions under disadvantageous conditions. For with distention of the stomach the diaphragm is elevated with resultant upward displacement of the heart. Even when the slight increase in vital capacity due to the compression of the lungs by the elevation of the diaphragm may be significant to the already distressed patient. It has already been mentioned (page 416) that Wayne and Graybiel found that individuals with angina pectoris have a smaller exercise tolerance after a meal. These observations supply the rationale of what many cardiac patients learn for themselves, namely, that they are dyspneic and oppressed following a large meal, and that anginal pain is especially apt to supervene at this time. In individuals with coronary arteriosclerosis, sudden death following a large meal is not rare.

In addition to the transitory increase in the work of the heart following an ample meal, the metabolic rate and consequently the work of the heart throughout the day are augmented by more abundant food intake. This has long been known from experiments on the effects of undernutrition in health, and has been brought out especially well in relation to the treatment of heart failure by the important studies of Master, Jaffe and Dack.[18] They kept 42 patients with coronary artery disease on a daily ration containing 800 calories (80 grams of carbohydrate, 50 grams of protein, and 30 grams of fat). In only 5 did the basal metabolic rate fall less than 10 per cent; in 6 it fell 10 to 14 per cent; and in the remaining 31 the metabolism fell more than 15 per cent, reaching −40 per cent in 2 patients and −30 per cent in 2 others. Master and his associates found that the low metabolic rates were attained after the patient had been maintained on the 800-calory diet for between two and four weeks; with increase in caloric intake, there was a similar lag before the metabolic rate rose.

The Value of Undernutrition in Heart Failure and Angina Pectoris.—Since undernutrition decreases the oxygen consumption of the body and consequently the work of the heart, one would anticipate that a diet of low caloric value would be well adapted to the treatment of heart failure and angina pectoris. Such a diet is in line with the general principle of maintaining the work of the heart at as low a level as feasible, the very principle that led to the intro-

duction of thyroidectomy (page 743). That restricted caloric intake is of value in the treatment of cardiac failure and angina pectoris was known to clinicians long before the theoretical basis was understood. As far back as 1866, Karell[15] introduced what has since been known as the "Karell cure," in which the total intake of the patient is limited to 800 cc. of milk daily. There is *every reason to believe that the Karell diet is of value merely* because it is a form of severe restriction of fluid, sodium chloride, and caloric intake. Experience has shown that the Karell diet forms an excellent method of initiating the treatment of severe heart failure or angina pectoris in other than undernourished individuals or those with active rheumatic fever. It forms a splendid adjuvant to bed rest and digitalis in the treatment of acute decompensation of various origins. Especially in plethoric individuals with hypertensive and arteriosclerotic disease, one often finds that *merely keeping the patient in bed with intake restricted to 800 cc.* of milk daily and a brisk purge accomplishes remarkable amelioration of dyspnea and other manifestations of heart failure.

After the treatment of severe heart failure has been initiated by two or three days on 800 cc. of milk daily, the patient may be given a diet containing between 800 and 1200 calories. The length of time which this low-calory diet should be continued depends on the circumstances of the case. In patients with hypertensive and arteriosclerotic heart failure, especially if they are obese, great *advantage may be derived by continuing the stringent dietary* restriction for a long period. Master, Jaffe and Dack kept many of their patients with coronary arteriosclerosis on diets containing between 800 and 1200 calories for between three and twelve months, during a large part of which they were ambulatory. None of these individuals developed acidosis or hypercholesterinemia, and there were no changes in the protein content of the plasma. Of course, there is loss of weight on low-calory diets, which is an advantage in obese patients. But if the undernutrition is protracted and the metabolic rate falls, *the loss of weight becomes less rapid.* Thus, a man of 188 pounds with angina pectoris due to coronary arteriosclerosis was put on complete bed rest with a diet of between 600 and 800 calories daily. His weight fell to 170 pounds in fifteen days. After that he was ambulatory, attending to business a few hours daily, and received between 1200 and 1500 calories. Nevertheless, at the end of eight months his weight was 166 pounds and was stationary.

The chief disadvantage of diets of very low caloric value is that weakness often develops and forces an increase in the energy value of the food. But more often the weakness passes, or is relieved by a comparatively small increase in the ration, and the patient can be kept indefinitely on a comparatively low food intake. Perhaps

largely because their activities are restricted, most patients with symptoms of heart failure maintain weight and strength on a diet of less than 2000 calories daily. The object should be to reduce the energy value of the food as much as is consistent with the maintenance of weight and strength, in obese individuals, of course, the former is desirable only after suitable reduction in body weight had been attained. There would appear to be no factual basis for the fear that undernutrition of this degree impairs the functional capacity of the heart.

The principal field of utility of low-calory diets is in hypertensive and arteriosclerotic heart disease, especially in the obese. Master and his associates obtained splendid results with such diets following coronary thrombosis; they kept their patients on the restricted diet for periods ranging over one year. Not only is heart failure due to hypertension or coronary arteriosclerosis most often favorably influenced by diets of low caloric value, but good results are often obtained in angina pectoris. When the cardiac pain occurs in obese individuals of plethoric appearance who have hypertension, coronary arteriosclerosis, and a very large left ventricle, rigid restriction of caloric intake is especially apt to be beneficial. In several such cases, following the institution of bed rest and a diet of 600 to 800 calories daily for two weeks, I have witnessed the disappearance of the pain for a considerable time. My impression is that rest and dietary restriction are most apt to help angina when the causative relative ischemia is due more to increase in the load and bulk of the left ventricle than when it is due almost entirely to coronary narrowing with a relatively small heart and normal blood pressure. Diets of low caloric value are often also of help in the treatment of heart failure associated with old valvular defects with or without auricular fibrillation. But in the presence of florid rheumatic infection, especially in children, the situation is different Here, the primary consideration is to combat the infection, and for this purpose an abundant diet seems best advised.

The low-calory diet should be well balanced In a previously well-nourished individual, a slightly negative nitrogen balance for a few weeks is not of great moment Vitamin deficiencies should be avoided. Small individual meals may be attained by more frequent feedings. The patient should be instructed never to eat so much that he feels full. Reduction in the bulk of the meals can be greatly facilitated by proper choice of foods. There is often a tendency to include too large a ration of bulky vegetables of low caloric yield which are not only initially of large volume but tend to produce flatulent distention. Often, cardiac patients who are uncomfortable as a result of the distention produced by a vegetarian or lacto-vegetarian diet are helped by the partial substitution of meat, eggs, fish, and other concentrated foods

A low-calory diet, with fluid and salt restriction, for cardiac patients may be along the following lines. But it is to be emphasized that the diet is to be chosen in accord with the idiosyncrasies of the patient; some, for example, are distended and uncomfortable when much milk is given, and this usually valuable food for cardiac patients must then be removed from the fare.

Breakfast:
 Fruit.
 Cereal
 1 egg.
 6 ounces of weak tea or coffee.

Mid-morning:
 6 ounces of milk with cracker.

Dinner:
 Boiled or broiled, tender meat, chicken, or fish.
 Vegetables.
 1 slice thinly buttered bread or toast.
 Gelatin dessert or stewed fruit.
 6 ounces of weak coffee or tea.

Mid-afternoon.
 6 ounces of milk with cracker.

Supper:
 Fish, chicken, egg, or cottage cheese.
 Salad with mineral oil dressing or vegetables.
 1 slice thinly buttered bread or toast.
 Light pudding or custard.
 6 ounces of weak coffee or tea.

Before retiring:
 6 ounces of hot milk or malted milk.

Patients subject to nocturnal paroxysms of cardiac asthma are usually better off if they take no food or fluid after supper.

High-carbohydrate Diet.—Smith, Gibson and Ross[24] have advocated the use in heart failure of a high-carbohydrate diet. The diet consists of 44 grams of protein, 110 grams of fat, and 220 grams of carbohydrate (2100 calories), which is augmented by such sugars as dextrin maltose, dextrose, and lactose. They believe that the easily available energy of the carbohydrates helps the heart and may also have a good effect on the congested liver. The writer has tried this diet without observing special benefit, and believes that the principle of caloric restriction sketched above yields better results in at least the great group of cases due to hypertension and arteriosclerosis In active rheumatic infection with fever, a higher protein ration would appear desirable to combat the nitrogen waste. However, in diabetics with coronary arteriosclerosis who are receiving insulin, a high carbohydrate ration is usually desirable to avert

the anginal phenomena that may be favored by even slight depression of the sugar content of the blood (page 584).

Restriction of Water and Sodium Chloride.—An essential part of the dietary management of heart failure is restriction of the intake of water and sodium chloride. When the dynamics of the circulation are so altered as to favor transudation from the blood stream into the tissues (see Chapter XII), this transudation will be the more abundant the larger the available supply of water and sodium chloride. Reducing the intake of water and sodium chloride thus tends to lessen the amount of edema resulting from cardiac insufficiency. This applies not only to right-sided failure with its manifest peripheral edema and transudation into the serous cavities, but also to isolated failure of the left side of the heart, in which the less obvious but more dangerous edema of the lungs occurs. In many cardiac patients without clinical signs of edema, loss of weight of as much as 10 pounds on fluid and salt restriction testifies to the existence of occult fluid retention. The excellent results of fluid and salt restriction in heart failure are doubtless due largely to the resulting resorption of edema. However, other factors may also enter. Since the different compartments of the body water are in equilibrium with one another, it is possible, though not yet demonstrated, that fluid and salt restriction in heart failure result in a decrease in blood volume secondary to the decrease in the volume of the interstitial fluids. Such a diminution in blood volume would doubtless have a salutary effect on heart failure through the intermediacy of decrease in the work of the heart. This conception is strongly fortified by the work of Grollman,[11] who found that the ingestion of water and more so of salt solution results in an increase in cardiac output; while the origin of the latter is not entirely clear, it is most likely due to increase in blood volume. In hypertensive patients, the occasional drop in arterial pressure following salt restriction is also welcome from the point of view of heart failure and angina pectoris.

In severe heart failure, the fluid and salt intake should be cut down sharply. This is attained in the Karell diet of 800 cc. of milk daily. As long as the symptoms of heart failure are severe enough to keep the patient in bed, unless there is fever due to an infection, the fluid intake should not exceed 1200 cc daily. The sodium chloride ration may be kept below 2 grams daily by instructing that no salt be added to the food and that no especially salty food be consumed. In patients with nocturnal attacks of cardiac asthma, it is well that no fluid be taken in the evening.

Occasionally, the fluid restriction and salt privation are carried too far in cardiac patients. As a result of long-continued fluid and salt restriction and the removal of large quantities of salt and water from the body by repeated mercurial diuresis, a state of

dehydration may result. The most common symptom of such a state, which I have repeatedly seen, is great weakness, but delirium and other manifestations often considered to indicate a "cardiac psychosis" may also develop. In several such cases, I have seen improvement of the weakness and mental state quickly follow the administration of water and sodium chloride.

Alcohol.—There is no evidence that alcohol specifically damages the heart. Most of the cases of what was known as "beer heart" and "wine heart" appear to have been essential hypertension, often combined with obesity; some of them may have been due to avitaminosis (page 596). Of course, it is undesirable for the cardiac patient to drink to excess, but an occasional small drink may be permitted to those who enjoy it. In angina pectoris, as Heberden pointed out, alcoholic drinks often afford considerable relief, presumably through causing vasodilatation. I have repeatedly seen patients who could avert anginal pain by taking whisky at the onset.

Tobacco.—The question of smoking by cardiac patients is one that should be decided for the individuals; there are no valid general rules. If the patient experiences palpitation, pain or other unpleasant symptoms, or it is found that the use of tobacco is followed by pronounced tachycardia, smoking should be discontinued. But if such symptoms do not arise, except perhaps for individuals with coronary artery disease, there would seem to be no well-supported reason for denying the patient who enjoys it the pleasure of smoking in moderation. Smoking produces extrasystoles in some persons, but they may prefer the annoyance to discontinuing tobacco. The question of the use of tobacco by individuals with coronary arteriosclerosis is one on which has been written *pro* and *con* (Moschcowitz[20] and White and Sharber[31]). That tobacco can produce arterial lesions seems to be demonstrated by thromboangiitis obliterans, but of course this does not indicate that it is also concerned in the genesis of arteriosclerosis. Cases have been reported in which coronary arteriosclerosis and thrombosis have been attributed to tobacco but in none of them is the evidence of the connection unequivocal. Harkavy[12] has found that smokers who develop coronary thrombosis relatively early in life exhibit a much higher incidence of positive skin reactions to tobacco than do smokers without cardiac disease. Whether this interesting finding indicates that allergy to tobacco is concerned in the pathogenesis of some instances of coronary thrombosis requires further investigation. Speaking strongly against the frequent significance of tobacco in the etiology of coronary arteriosclerosis is the detailed study of White and Sharber. They found a smaller proportion of excessive smokers and a high incidence of total abstainers from tobacco in 750 patients with angina pectoris than in 750 controls of similar age and walks of life. However, one not rarely encounters individuals with angina pectoris due to

coronary arteriosclerosis who have fewer attacks when they abstain from smoking and very rarely cases in which cessation of smoking is followed by freedom from cardiac pain for protracted periods. In such cases, of course, smoking should be discontinued

OBESITY

Effects of Obesity on Circulation and Respiration.—Obesity constitutes a handicap to circulation and respiration which is documented in the shortness of breath of stout individuals. Among the factors concerned are the following:

1. As a result of the increase in intra-abdominal fat, the diaphragm is elevated with decrease in lung volume. Bowen[1] found that in obesity the vital capacity is decreased an average of 20 per cent, and in very fat persons the diminution is much more. In obesity respiration is less efficient, being more rapid and shallow and accelerating more during exercise, than in those of normal weight (Prodger and Dennig[22]). It seems probable that the alterations in the mechanics of respiration are the chief cause of the exertional dyspnea of obese persons without intrinsic cardiovascular disease.

2. Great obesity also affects the organs of circulation directly. As a result of the high position of the diaphragm the heart is displaced upward and assumes a more horizontal position with rotation of the electrical axis to the left. It seems plausible, although precise information is not available, that the change in the position of the heart is a handicap, especially when the heart is called upon for increased work during exercise or when the organ is enlarged Prodger and Dennig found that the standing pulse rate of the obese averages higher than in those of normal weight.

A moot question is that of the significance of the large subepicardial fat deposits usually present in the obese (*obesitas cordis*). These masses of fat pass between the muscle fibers and in extreme instances extend in places in the right ventricle all the way through to the endocardium. In the past these subepicardial fat deposits were highly esteemed as causes of heart failure. However, they are often found at the necropsy of obese individuals who had no evidences of heart failure. While not proven, it is conceivable that in cases in which the fat deposits extend completely through the right ventricle, they may be the cause of the otherwise unexplained sudden deaths which occur on very rare occasions in obese persons (*cf.* Smith and Willius[25]). But in all such cases careful search for coronary artery disease should be made. It should be borne in mind that the excess of subepicardial fat which is part and parcel of general obesity is independent of fatty change in the heart muscle fibers.

3. In considering the effect of obesity on the work of the heart,

one must differentiate between rest and exercise. The available data indicate that at rest obesity causes little if any increase in the work of the heart. For usually the blood pressure is unchanged and Prodger and Dennig found with the acetylene method that the cardiac output averaged the same (3.7 liters per minute) as in their normal controls; per square meter body surface, the cardiac output averaged a little less than in the controls. That the work of the heart at rest is not augmented in obesity is also indicated by the old observation of Hirsch[13] that the muscle mass of the heart in obesity is small in comparison to the body weight. The absence of increase in cardiac output in obesity presumably means that there is little blood flow through the fat tissue, although there may be also some decrease in blood flow through the other tissues.

During such exercise as walking, on the other hand, the work of the heart is doubtless increased in obesity, for the muscles must move a larger mass. Indeed, Prodger and Dennig found that in obesity oxygen consumption is increased during exercise more than corresponding to the extra weight. Apart from the unlikely eventuality that the greater oxygen consumption is covered entirely by an increase in the arteriovenous oxygen difference, there must be a greater increase in cardiac output during exercise in the obese than in those of usual weight. The resulting increase in the work of the heart may play a part in the exertional dyspnea of the obese. That the circulation does not accommodate itself to exercise as well in the obese as in those of normal weight is also shown by the finding of Lichtwitz[16] and of Prodger and Dennig that the lactic acid content of the blood rises much higher during exercise in the obese. Whether the increase in the lactic acid content of the blood is quantitatively sufficient to be of significance in the pathogenesis of exertional dyspnea remains to be determined.

Therapeutic Utility of Weight Reduction in Heart Failure.—Since obesity lessens the vital capacity, increases the work of the heart during exertion, and perhaps impairs the functional capacity of the heart, it is not surprising that reduction in body weight is often a valuable measure in the treatment of cardiac failure in the obese. Indeed, loss of weight generally increases the exercise tolerance of the obese with healthy hearts, and this may be even more marked in those with cardiac insufficiency. Especially in obese individuals with hypertensive and arteriosclerotic heart disease, weight reduction is often accompanied by notable symptomatic improvement and is almost always indicated. Obesity is a less common accompaniment of rheumatic heart disease but does occur, especially in middle-aged women, and here also reduction may be a valuable measure. Striking improvement from weight reduction is perhaps most often seen in the not uncommon cases in which the first symptoms of heart failure accompany or soon follow great gain

in weight, and in which it seems likely that increasing obesity is the precipitating cause of the cardiac insufficiency. Obesity is so deleterious to individuals with heart disease that it would appear indicated to attempt to reduce body weight in all obese persons with heart disease, even though they have no symptoms of cardiac failure or angina pectoris, purely as a prophylactic measure to defer the onset of the symptoms.

Most often, weight reduction in individuals with heart disease is to be accomplished, as far as possible, by a low-calory diet alone, without the aid of increased exercise or the administration of thyroid extract. Frequently, it is wiser to carry out the reduction with the patient in bed. The technic of low-calory diets in heart disease has already been discussed (page 678).

Only exceptionally is considerable increase in exercise to be prescribed for cardiac patients as an aid in weight reduction Exercise comes into question principally in individuals with hypertension or a cardiac lesion which, despite the fact that they are asymptomatic, have resulted in the patient becoming so apprehensive of exertion that lack of exercise plays an important part in the genesis of the obesity. In such individuals, carefully controlled walking, golf or massage may be of great value.

Apart from instances of true myxedema heart (page 590), thyroid extract should be invoked against obesity only in rare cases in which the metabolic rate is definitely subnormal and even very low-calory diets make little impression on the body weight. I have seen but few cardiac patients in whom the administration of thyroid seemed advisable to help reduce weight; these were almost all middle-aged women with hypertension and sometimes coronary arteriosclerosis, and it is quite likely that some cases in which marked loss of weight and symptomatic improvement were obtained were actually *formes frustes* of the myxedema heart I have known instances in which the administration of thyroid to obese individuals with arteriosclerotic or hypertensive heart disease seemed to be the provocative agent of severe heart failure or angina pectoris

SURGICAL OPERATIONS

The physician is often confronted by situations in which surgical operation is indicated in cardiac patients When this occurs, it is necessary to evaluate carefully whether the probable advantages to be derived from the operation outweigh the risks. In some cases, of course, the decision is easy; fulminant appendicitis or ectopic gestation may necessitate immediate operation despite severe heart failure On the other hand, there are many situations in which the judicious physician will refrain from operation where in an individual with a healthy heart he would advise operation, for

example, a pelvic repair in the presence of a failing hypertensive and arteriosclerotic heart.

Statistics regarding the mortality following operations in cardiac patients vary widely; one reason is doubtless difference in the character of the material analyzed. In 170 patients with heart disease who underwent operation, Sprague[24] found a mortality of 24.7 per cent; in 494 operations on cardiacs studied by Butler, Feeney and Levine,[4] the mortality was 12.1 per cent. Such figures, of course, tell us little, for some of the deaths had nothing to do with the presence of heart disease and some would have occurred even if the operation had not been performed. Of their mortality of 12.1 per cent, Butler, Feeney and Levine consider that 6.3 per cent might not have occurred if the operation had not been carried out; this includes the deaths from cardiac failure, postoperative pneumonia, embolism and other causes which *may* have been connected with the heart disease.

The two factors which are of the greatest importance in determining the added risk of operation in individuals with heart disease are the functional capacity of the heart and the state of the coronary arteries.

Experience shows that in the absence of heart failure well-compensated rheumatic valvular lesions add little to the risk of operation. It is especially to this class of patient, notably when young, that the statement of Marvin[17] applies: "A damaged heart, whatever its physical signs, is the equivalent of a normal one for anesthesia and operation if it is carrying on an adequate circulation under normal conditions of life, with the possible exception of the syphilitic heart." And even patients with well-compensated syphilitic heart disease tolerate operation comparatively well, though presumably narrowing of the coronary orifices constitutes an added risk; in 14 operations on 11 patients with syphilitic aortic regurgitation, Butler, Feeney and Levine had 1 unexpected death. In well-compensated hypertension, operations are generally well borne as long as there is no renal insufficiency; the latter adds greatly to the risk of operation. In the experience of the writer, patients with renal insufficiency are on the average much worse operative risks than those with heart failure. With proper preparation, the operative mortality in thyrotoxic heart disease is very small (page 788).

The presence of heart failure adds a risk to operation. It is not so much the danger of death during the operation, although this occurs on rare occasions as a result of heart failure or embolism, as the greater incidence of postoperative pulmonary complications. It is to be presumed that the passive congestion of the lungs present in the left-sided heart failure of mitral and aortic valvular lesions, hypertension, and coronary arteriosclerosis predisposes to the pul-

monary atelectasis which probably forms the basis of at least a considerable proportion of cases of postoperative pneumonia. Moreover, patients with right-sided heart failure are more liable to thrombophlebitis of the lower extremities with its risk of late embolism. Sometimes, heart failure becomes progressively worse after operation. Auricular fibrillation may be initiated during operation or shortly after, but is usually transitory.

The risk of operation is also increased by the presence of angina pectoris and coronary arteriosclerosis (*cf.* Master, Dack and Jaffe,[19] Brumm and Willius[2]). While the large majority of such individuals pass through operation without circulatory trouble, coronary thrombosis develops in the days after operation with less rarity than would be anticipated if it were purely a coincidence. The same is true of sudden death during or after operation; only some of these deaths are explained at necropsy by embolism, others are perhaps due to ventricular fibrillation or other disturbance in the mechanism of the heart beat.

Patients with heart failure should be adequately digitalized before operation. That every effort should be made to lessen the duration and shock of an operation on a cardiac patient goes without saying. After the operation the attempt should be made to lessen the chances of pulmonary atelectasis by moving the patient and perhaps administering carbon dioxide, and of thrombophlebitis of the lower extremities by motion and massage. In cardiac patients one should be especially careful to avoid overloading the heart with excessive intravenous infusions. I have several times seen pulmonary edema produced in this fashion.

The anesthesia is, of course, of the greatest importance One would presume that, when feasible, local would be preferable to general anesthesia However, in the operations on cardiac patients reviewed by Butler, Feeney and Levine, the mortality was about the same with both local and general anesthesia. When general anesthesia is used, the skill of the anesthetist is perhaps more important than the choice of the anesthetic It is most important to minimize the pre-operative fear of the patient and, by skilful induction, to avoid struggling before anesthesia is attained. There is no general agreement on which of the general anesthetics is preferable for cardiac patients Marvin considers ethylene as best suited, with nitrous oxide and oxygen as second choice, and ether as less desirable. Cyclopropane is sometimes excellent

PREGNANCY*

The question often arises whether a woman with heart disease should be allowed to bear a child, and what should be done when one with a cardiac disorder becomes pregnant. Discussion of

* Jansen[14] has published a detailed monograph on the heart in pregnancy

these problems may be prefaced by a few remarks concerning the effect of pregnancy on the normal heart.

The Cardiac Load in Pregnancy.—During pregnancy, the work of the heart increases. The latter is roughly proportional to the product of the mean arterial pressure and the cardiac output. During normal pregnancy the mean arterial pressure changes comparatively little; there is usually a rise in pulse pressure due mostly to fall in diastolic tension. On the other hand, investigations by Gammeltoft,[9] Stander and Cadden,[27] and Burwell[3] have shown that there is a pronounced increase in cardiac output, which generally reaches close to 50 per cent in the ninth lunar month. Peculiarly enough, the elevated cardiac output diminishes somewhat in the last weeks of gestation.

The increase in cardiac output renders feasible the great augmentation in blood flow through the uterus without depletion of the other organs. This accomplishment is also facilitated by accompanying rise in circulating blood volume, which in the observations of Thomson[29] and his associates averaged 42 per cent. The correlation of the changes in cardiac output and blood volume is indicated by the finding that both fall in the last weeks.

The mechanism of the increase in cardiac output during pregnancy is not altogether clear. Burwell has pointed out that the increase is greater than can be accounted for by the augmented oxygen consumption, for the arteriovenous oxygen difference is decreased There are also such other evidences of accelerated circulation as faster basal pulse rate, increased pulse pressure with somewhat collapsing pulse, and increased velocity of blood flow (Cohen and Thomson[6]). Like behavior of the circulation occurs in arteriovenous fistula (page 579), and Burwell has advanced the ingenious suggestion that in pregnancy the placenta, in which wide shunts connect the arterial and venous sides of the circulation, acts like an arteriovenous fistula.

In addition to the burden imposed by the greater cardiac output, it is possible, though not proved, that the upward displacement of the heart in the later months also constitutes a handicap. This displacement is probably the cause of the tendency to rotation of the electrical axis to the left and occasional development of large Q_3 and inverted T_4 waves The seeming enlargement of the heart is probably also almost entirely a manifestation of displacement as pregnancy progresses.

As a result of these factors and the greater weight, women in the later months of pregnancy become dyspneic at lower levels of exertion than usual. This occurs despite a normal vital capacity (Cohen and Thomson). Not rarely, there arises a clinical picture reminiscent of the effort syndrome; it includes exertional dyspnea, tachycardia, simulated enlargement of the heart because of dis-

placement upward and forward against the chest wall, a systolic murmur, and accentuation of the pulmonic second sound. Of course, there may also be edema of the feet; Burwell has shown that this, as well as the development of varicosities, is favored by increased venous pressure in the lower extremities due principally to pressure by the enlarged uterus. It is important that this syndrome should not be confused with organic heart disease Indeed, Gammeltoft[9] states that diastolic murmurs may arise during pregnancy in the absence of organic heart disease, an observation that I have not made other than in severe anemia

During labor, the heart is further burdened by the considerable rise in arterial pressure that occurs during the pains.

Despite these strains, the previously healthy heart does not fail during pregnancy or labor, apart from rare instances of acute left ventricular failure due to sudden rise in blood pressure manifesting the toxemia of pregnancy.

Management of Heart Failure in Pregnancy.—As just intimated, only the previously diseased heart fails as a result of pregnancy. In fact, recent studies have shown that even women with antecedent cardiac disease develop heart failure during pregnancy in a far smaller proportion of cases than was formerly believed, and further that such failure is fatal much more rarely than had been thought. Some of the older statistics purported to show that one-half or more of women with cardiac lesions succumb during pregnancy. These figures were undoubtedly obtained by including only those women with cardiac lesions who also had heart failure. It is now known that the course of cardiac disease in pregnancy is determined not especially by the nature of the cardiac lesion (apart from bacterial endocarditis) but almost entirely by the functional capacity of the heart at the start of pregnancy. This has been brought out in all recent investigations, but with especial clarity by the excellent studies of Pardee.[21] Using the functional capacity of the heart at the onset of pregnancy as a criterion, he divided the cases into four groups in accord with the classification of the New York Heart Association:

CLASS 1.—Those with cardiac lesions but no evidences of failure on even considerable exertion. Of 157 such patients, none died

CLASS 2 *A*.—Those whose activitiy is slightly limited by dyspnea, etc., on exertion. Of 180 such patients, 1 died.

CLASS 2 *B*.—Those whose activities are greatly limited by cardiac insufficiency. Of 169 such patients, 8 died.

CLASS 3.—Patients who are entirely or largely bed-ridden. Of 40 such patients, 16 died.

From Pardee's figures (*cf.* also the statistics of Carr and Hamilton[5] and Stander and Kuder[28]), it is evident that the woman with a faultlessly compensated cardiac lesion—in over 90 per cent of the

cases it is rheumatic heart disease that comes into question—takes, statistically speaking, very little chance of losing her life during pregnancy. However, there is some danger. This is shown by the fact that one occasionally encounters acute pulmonary edema in pregnant women with mitral stenosis who had no symptoms of heart failure before pregnancy and did not even know that they had a cardiac lesion. And other patients with valvular lesions gradually develop symptoms of heart failure as pregnancy proceeds or during labor. Nevertheless, with proper management, the chances that a woman with well-compensated rheumatic heart disease will pass through pregnancy with little or no trouble are so great that the physician is not justified in refusing permission for pregnancy, or interrupting it once it has occurred, if the woman wants a child and there are no sociological contraindications. Whether pregnancy abbreviates the life of women with heart disease who pass through labor successfully remains to be decided. The statistics of Reid[23] speak against pronounced shortening, for he found that married women (with an average of 5.75 children) with heart disease died at an average age but little less than that of unmarried cardiac women

Much more difficult is the situation when the woman has or has had slight symptoms of heart failure. She should be informed that she is taking a definite risk and that interruption of pregnancy, apart from religious considerations, is justified. In deciding whether or not to permit pregnancy in a woman who is dyspneic on mild exertion, one must take into account all the facts in the case, including the desire of the patient for a child, whether or not there are already children, the financial position of the husband in relation to the ability of the mother to rest during pregnancy and to have her household work done by another after pregnancy, the obstetrical status with regard to the probable ease of delivery, and the age of the patient. Younger women with cardiac disease generally do better in pregnancy than older. If it is decided to go ahead with pregnancy, the patient should be warned that she will have to rest a great deal. A large part of the last months of pregnancy should be spent in bed; exertion and excitement are to be avoided as much as possible. The diet should be poor in salt and the fluid intake restricted, but a full ration of protein is to be allowed because of the tendency to hypoproteinemia and edema in pregnancy. If there are evidences of heart failure the patient is to be digitalized. Should it become evident in the last months that heart failure is progressing, it is usually wise to deliver prematurely. The technic of the premature delivery should of course be left to the obstetrician, who will choose the method promising the briefest and easiest labor. In some cases, Cæsarean section is the procedure of choice

Women presenting evidence of severe heart failure—dyspnea on slight exertion, paroxysmal dyspnea, edema, swelling of the liver, etc.—should not become pregnant. Not only are they running a considerable danger, but there is also a strong possibility that they will not have a live baby; according to the statistics of Fellner,[3] women with cardiac decompensation have an abortion or premature labor in 20 to 45 per cent and a stillbirth in 26 to 40 per cent of the cases. If women with manifest heart failure are seen early in pregnancy, they should be aborted If they are first seen in the fifth or sixth months and are anxious to have a child, the attempt may be made to carry them along until the period of viability. It is necessary to do the same in patients seen early who refuse abortion for religious or other reasons The woman should be kept in bed with digitalis and other treatment for the heart failure; one is sometimes surprised how severely decompensated a patient may be in the fifth or sixth month and yet improve sufficiently under appropriate treatment to have a live baby. Even if the bed rest and other measures result in great improvement it is rarely wise to allow the pregnancy to proceed to the end; delivery should be induced when the baby is viable. In women who are first seen when badly decompensated, it is generally judicious to attempt to improve the state of the circulation before emptying the uterus. As in the preceding group of cases, the method of delivery is to be left to the obstetrician, but in a higher proportion Cæsarean section under local anesthesia is indicated; version and other intrauterine manipulations are to be avoided but shortening of the second stage of labor with forceps after full dilatation is often wise One competent to meet emergencies of cardiac origin should be present during the delivery.

A complication of mitral stenosis in pregnancy worthy of special mention is acute pulmonary edema It may come on suddenly, out of a seemingly clear sky, and may prove fatal, although some patients have repeated attacks during a pregnancy One woman had three such attacks, each following intercourse. Morphine should be administered and, if the situation appears threatening, venesection performed. Especially if the patient is in the hospital, oxygen may be administered.

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CHAPTER XXXIV

THE TREATMENT OF HEART FAILURE: II DIGITALIS

Few indeed are the patients with heart failure in whom digitalis is not indicated at one time or another. While not always successful, indeed sometimes contraindicated, digitalis may be life-saving and often restores otherwise hopelessly bed-ridden individuals to long years of usefulness which could not be attained by any other means at our command. The beneficial effects of digitalis are so specifically confined to the alleviation of heart failure that when symptomatic improvement results from the administration of the drug, the inference is justified that the symptoms in question were directly or indirectly due to cardiac insufficiency.

Despite ceaseless investigation since the days of Withering,[81] the action of digitalis is not altogether understood. Recent studies have shown that this action is even more complex than was formerly realized; multiple mechanisms with different points of attack participate in the relief of heart failure by digitalis, and their individual importance varies in the diverse forms of cardiac insufficiency Broadly speaking, it may be said that digitalis tends to relieve heart failure in two general ways:

First, and by far the more important, through increasing the functional capacity of the heart

Second and of significance yet to be established, through decreasing the venous return and consequently the work of the heart.

Before describing how these effects are manifested clinically, it may be well to review briefly the pharmacological observations on animals which form a large part of the basis of what is known concerning the therapeutic action of digitalis

THE ACTION OF DIGITALIS ON THE PROPERTIES OF THE HEART MUSCLE

Experimental investigations* have shown that digitalis affects the activity of the heart not only through direct action on the myocardium but also through stimulation of the nervous inhibitory mechanism. Since Traube[82] first found that the bradycardia produced by digitalis can be counteracted by cutting the vagi, the nervous inhibitory effects have been attributed to the action of digitalis on the vagus nerve. Most of the older investigators

* The following discussion applies only to the warm-blooded heart, for a classical description of the action on both the amphibian and the mammalian organisms the reader is referred to Cushny[13]

considered that the glucosides in question stimulate the vagus center, but the later work of Straub[78] indicated rather that digitalis raises the sensitivity of the heart muscle to the physiological vagus tone Recently, however, the investigations of Heymans[40] and his associates have shown that this is not the whole story. By beautiful cross-circulation experiments on the dog with their well-known "isolated head" preparation—which enables them to perfuse independently the brain and the carotid sinus—they found that perfusion of the vagus center with digitalis does not inhibit the heart. On the other hand, perfusion of the carotid sinus with the drug produces the characteristic cardiac inhibition. Heymans and his co-workers further found that the application of strophanthin to the carotid sinus results in a more pronounced slowing of the heart from a given rise in arterial pressure. From these experiments it seems fair to conclude that the nervous inhibition of the heart by digitalis is due not only to sensitization of the heart muscle to vagal tone but also to action on the carotid sinus and aorta with resultant *reflex* increase in vagal and decrease in sympathetic tone.

The summation of the direct muscular action of digitalis and the nervous inhibition of the heart by the drug results in the following effects:

(*a*) The muscle is stimulated, *i e*, *the force of ventricular systole* is increased. Gold and Cattell[27] measured the tension developed by the cat's papillary muscle suspended in Ringer's solution or blood and found that digitalis glucosides reversed the direction of falling systolic tension while the diastolic tension was maintained constant. This finding shows that digitalis bodies increase the force of contraction of the mammalian myocardium by direct action on the muscle. The same is demonstrated in the heart-lung preparation by the development of higher maximal intraventricular pressure starting from the same diastolic filling, and by more complete emptying of the ventricle. Schaefer[72] found that in the heart-lung preparation, the heart of a cat which had previously been digitalized could empty itself against an arterial pressure averaging 22 mm.Hg more than the maximum for an undigitalized heart. Furthermore, when the arterial resistance or venous return is increased in the heart-lung preparation, digitalis enables the heart to perform the greater work with a smaller increment in diastolic filling (Bijlsma and Roessingh[4]). The force of auricular systole is also augmented by doses of digitalis that are not too large. But when sufficient of the drug is given, the stimulating effect on the auricular muscle is more than counterbalanced by the effect of vagal inhibition, with the result that, in the dog, the strength of the contractions is reduced and auricular standstill in the diastolic position may occur (Cushny[19])

(*b*) With vagal inhibition functioning, digitalis generally, though apparently not always, produces greater *diastolic volume* of the

heart. To some extent this is doubtless due to the slowing of the heart resulting from vagal inhibition, which allows more time for diastolic filling. There has been difference of opinion regarding the effect of digitalis on the amplitude of diastole in the isolated heart not under vagal control. Cushny's myographic tracings indicated that in the absence of vagal inhibition the extent of relaxation in diastole is unchanged or may occasionally be slightly reduced. But the best available data appears to be that of Wiggers and Stimson,[87] working with sensitive optical registration and controlling the heart rate and arterial resistance. They found that the increased systolic discharge produced by digitalis is accompanied by larger *diastolic volume, i. e., diastolic dilatation.* In Wiggers and Stimson's experiments there was no constant change in diastolic intraventricular pressure, the greater diastolic volume was sometimes accompanied by a rise, sometimes by a fall, in intraventricular pressure.

(*c*) As a result of the direct muscular action of digitalis, both the contraction and the relaxation of the ventricle take place more rapidly. The total *duration of systole* is abbreviated, with the result that the *diastolic rest period* forms a larger fraction of the cardiac cycle even when, as a result of vagotomy or atropinization, the rate is not slowed by digitalis.

(*d*) The effect of digitalis on the *rate* of the heart in the experimental animal is almost entirely through vagal inhibition The changes in rate of the isolated heart following the administration of other than excessive doses of digitalis are insignificant compared to those when vagal inhibition is functioning. Cushny states that the rate of the isolated heart is unchanged, while other investigators (Weese[84]) find with small quantities of digitalis a slight acceleration due to sinus stimulation and with larger amounts a small slowing of the sinus rate In the intact animal digitalis slows the heart through vagal inhibition of the sinus by the mechanisms described above (page 694); that this slowing is of vagal origin is shown by the fact that it does not occur after atropine. With larger doses of digitalis the auriculo-ventricular block to be described in the next paragraph may result in dropped beats and thus contribute to the slowing of the ventricle. However, with doses of such magnitude as to produce severe disturbance of auriculo-ventricular conduction or complete dissociation, ventricular ectopic beats may be so numerous as to produce a rate above the normal.

In patients with heart failure, the slowing produced by digitalis is due not only to the vagal effects seen in the experimental animal but also to some extent to extravagal mechanisms (page 698)

(*e*) Digitalis depresses *conductivity* through both direct action on the muscle and vagal inhibition. This is the effect of the drug that

accounts, in the main, for its triumphs in auricular fibrillation (page 710) The retardation of auriculo-ventricular conduction that results from small or moderate doses of digitalis in the healthy heart appears to be mainly due to vagal inhibition. For Cushny found in the dog that such doses of digitalis do not alter the conduction time along the bundle of His if vagal inhibition is excluded by atropine. But that even under these circumstances conduction is also impaired by the direct muscular action of the glucosides is shown by the demonstration by Lewis, Drury and Iliescu[47] that if the auricular rate is greatly accelerated by electrical stimulation—thus simulating the state of affairs in human auricular fibrillation—the depression of conduction by digitalis bodies becomes manifest They interpret their findings as indicating that under these circumstances digitalis bodies depress conduction, not by slowing the rate at which the fibers conduct the impulses, but rather by an increase in the refractory period of the junctional tissues In the later stages of strophanthin poisoning Lewis and his associates found intra-auricular block of similar origin, and De Boer[14] has found that the spread of the excitation wave through the ventricular muscle is likewise hampered With sufficiently high doses of digitalis, complete auriculo-ventricular block is produced by the direct action of the drug on the junctional tissues.

(*f*) Apparently as a result of a direct action on the heart muscle favoring stimulus formation, digitalis may evoke ectopic beats of ventricular, junctional, or auricular origin. While the genesis of such ectopic beats is doubtless favored by slowing of the heart, the latter is not the fundamental cause, for digitalis may elicit them in the absence of slowing The production of ectopic rhythms by digitalis is further discussed on page 724.

(*g*) Because of the uncertainty regarding the existence of true diastolic tone in the mammalian heart (page 305), the question of the effect of digitalis on the tone of the heart will not be discussed here, the literature is reviewed by Weese.[84] It may, however, be pointed out that the frequent statements in clinical literature that digitalis augments the "tone" of the human heart really are based on no more than the observation that the heart diminishes in size under the influence of the drug. But such decrease in the volume of the heart does not necessarily indicate augmented diastolic tone in a strict sense, it may result from diminution in venous return (page 702) or increase in the functional capacity of the myocardium by virtue of which the heart can perform the same amount of work starting from a smaller diastolic volume.

(*h*) Digitalis increases the mechanical efficiency of the heart (page 711)

CORONARY BLOOD FLOW

Most of the older investigators (Cushny[13]), working on the isolated heart or excised coronary arteries, found that digitalis constricts these vessels. But the doses used were far above those applied in human therapeutics On the basis of well-controlled study on intact animals, Gilbert and Fenn[25] found evidence indicating, as they put it with appropriate caution, "that digitalis bodies may exert a vasoconstrictor action on the coronary arteries" This effect was apparently at least partly due to stimulation of the vagus, which is a coronary constrictor, for it was absent after vagotomy or atropinization Hochrein's[41] measurements of coronary flow with the thermostromuhr disclosed only slight changes as a result of digitalis. Ginsberg, Stoland and Siler[26] found in the heart-lung preparation of the dog that digitalis most often decreases coronary flow for about ten minutes, which is generally followed by an increase lasting for the duration of the experiment In the intact dog they observed no constant effect; they did not regard the changes observed as of magnitude sufficient to cause much disturbance of cardiac function It would not appear to have been demonstrated beyond doubt that digitalis in therapeutic doses significantly affects coronary blood flow. It is to be borne in mind that a drug may influence coronary flow not only through direct action on the vessels but also through the intermediacy of changes in the rate and mode of contraction and relaxation of the heart. Rein[64] found that the coronary blood flow is most abundant in relation to the work of the heart when the rate is slow and the stroke volume large A direct constrictor effect of digitalis on the coronary arteries might thus be more than neutralized by the slowing due to the drug

THE SIZE OF THE HEART

One of the most constant effects of digitalis is that it diminishes the size of the heart. This has been demonstrated under a variety of circumstances by accurate methods. In the heart-lung preparation Bijlsma and Roessingh,[4] Cohn and Steele,[11] and others have shown that when the heart starts to tire and dilate, the administration of digitalis diminishes in size. In the intact animal Cohn and Stewart[12] have shown by radiographic measurements of the surface area that digitalis diminishes the size of the heart; they found *this to be the case in both normal animals without cardiac* enlargement and in those in whom the heart was enlarged as a result of experimentally produced mitral regurgitation or auricular fibrillation

In man, Stewart and Cohn[77] have shown by measuring the area of the cardiac silhouette that digitalis diminishes the size of the heart, both in health and in the presence of cardiac enlargement

and heart failure In their healthy subjects the decrease in the surface area of the heart amounted to between 7 and 15 per cent and was at its maximum between four and twenty-four hours after the administration of the drug. As the effect of the digitalis wore off, the heart returned to its normal size, a process which sometimes took more than two weeks. It is to be emphasized that the diminution in the size of the heart due to digitalis is rarely as pronounced as to be immediately obvious in serial teleoroentgenograms; careful technic is necessary to demonstrate them. A seemingly striking diminution in the size of the heart during digitalis therapy is often due mostly to relief of meteorism and shrinking of an engorged liver, as a result of which the diaphragm descends and the heart occupies a more vertical position

THE RATE OF THE HEART

The effect of digitalis on the rate of the isolated heart and that of the intact experimental animal has already been discussed (page 695) In considering the effects on the heart rate in man, patients with auricular fibrillation or flutter are to be differentiated from those with sinus rhythm. In auricular fibrillation with accelerated ventricular rate, the latter is almost always reduced to normal, or even down to 40 or 50 beats per minute, by adequate doses of digitalis. In auricular flutter, also, digitalis generally diminishes the ventricular rate strikingly. Under both these circumstances the slowing is due predominantly to the impairment of auriculoventricular conduction, so that fewer stimuli from the fibrillating or fluttering auricles bombard the ventricles. In addition, the improved function of the ventricles due to this slowing and to the direct action of digitalis on the ventricular musculature—a factor strongly emphasized by Luten[49]—entails an additional slowing of the ventricular rate due to elimination of that portion of the tachycardia which is due to the heart failure itself (see below).

In the presence of normal sinus rhythm, on the contrary, the effects of digitalis on the heart rate are neither so striking nor so constant. Mackenzie[52] pointed out that in patients with normal rhythm digitalis most often has little effect on the rate, but that exceptionally pronounced slowing results. In only 1 of 12 patients with sinus rhythm did Cohn and Fraser[9] detect slowing prior to the onset of toxic symptoms of digitalization, while 5 others developed slowing subsequent to the appearance of rather severe toxic manifestations. Following a single dose of 1 minim of tincture of digitalis per pound body weight, Pardee[60] observed slowing of 10 or more beats per minute before the onset of changes in the *T* wave in 3, coincidently with the alterations of the *T* wave in 4, and subsequently in 2 of the 9 patients studied. In children with

regular rhythm the effects of digitalis on the heart rate are more pronounced than in adults; Sutherland[81] and McCulloch and Rupe[50] regularly observed marked slowing of the pulse in children with rheumatic heart disease following full therapeutic doses

To a large extent the degree of slowing produced by digitalis in sinus rhythm depends on the circumstances in which it is given. In patients in whom there is sinus tachycardia due to causes other than heart failure—for instance, in neurocirculatory asthenia, fever, or hyperthyroidisim—therapeutic doses of digitalis generally cause little or no slowing. On the other hand, when sinus tachycardia is a manifestation of heart failure, presumably functioning as a compensatory mechanism (page 293), digitalis most often causes definite and sometimes pronounced slowing of the pulse In such patients I have repeatedly seen slowing of about 30 beats per minute within forty-eight hours. The explanation of the pronounced slowing in some patients with cardiac insufficiency is perhaps that in addition to the direct effect of digitalis, the alleviation of heart failure removes a factor which has evoked acceleration of the heart; the slowing is thus both one of the causes and one of the effects of the success of the digitalis therapy.

THE CARDIAC OUTPUT

It was long accepted that digitalis in therapeutic doses always increases the volume of blood pumped per minute by the heart. This belief was largely an inference from the action of the drug in heart failure but was also supported by some animal experiments Thus, Cushny found by measurements with the cardiometer that with suitable doses of digitalis the increased power of the individual contractions more than atones for the slowing of the rate, with the result that the cardiac output is increased 20 or 30 per cent On the other hand, he found that with excessive doses the slowing predominates and the cardiac output falls below that before the administration of the drug

More recent studies have revealed, however, that the problem of the effect of digitalis on cardiac output is more complicated than would be inferred from these experiments, depending not only on the cardiac but also on the extracardiac actions of the drug, and further on the state of the circulation when the glucosides are administered Most important of all has been the demonstration that digitalis may have a diametrically opposite effect on cardiac output in health and in heart failure. *In health digitalis diminishes cardiac output, while in heart failure it may increase the volume of blood pumped by the heart.*

Effect of Digitalis on Cardiac Output in Health.—The important though seemingly paradoxical fact that digitalis diminishes cardiac

output in health was brought out by the pioneer investigation of Harrison and Leonard.[25] Using a direct method for determining the cardiac output based on the Fick principle, they found that following the intramuscular injection into the dog of a "full therapeutic dose" of digitalis the cardiac output decreased an average of 25 per cent. Smaller doses caused lesser and larger a greater decrease in cardiac output The maximum decrease appeared about six hours after injection and lasted for about forty-eight hours; the cardiac output then gradually rose, reaching normal in about six days

Similar observations were made in normal men by Burwell, Neighbors and Regen.[6] They found that the administration of from 1.4 to 2.7 grams of digitalis leaf was followed by a fall in cardiac output to an average of 84 per cent of the previous level. With the development of nausea, the cardiac output rose to 94 per cent of the normal level and with the subsidence of this symptom again declined to 82 per cent. The decrease in cardiac output was proportionately greater than the slowing in rate, the stroke volume being diminished. Burwell and his associates determined the minute volume by the carbon dioxide method of Field *et al.*, which yields absolute values that are too high, but doubtless reveals the direction of changes in cardiac output in individuals without pulmonary engorgement. Furthermore, the findings of Burwell and his co-workers have been confirmed by Stewart and Cohn,[17] using the acetylene method. They found the maximal decrease in cardiac output between four and twenty-four hours after the oral administration of digitalis, at which time the minute volume was reduced In the light of these findings, and other confirmations, it may be accepted that in the absence of heart failure digitalis diminishes the cardiac output.

Effect of Digitalis on Cardiac Output in Heart Failure.—The effect of digitalis on the output of the failing heart has been studied on the heart-lung preparation and in the intact experimental animal as well as in man.

In the heart-lung preparation, cardiac failure is documented by dilatation of the heart and rise in the pressure in the right auricle, while the output of the heart either falls or remains constant. In the heart-lung preparation presenting these criteria of failure, Cohn and Steele[11] and Anitschkow and Trendelenburg[1] have shown that digitalis and strophanthin increase the cardiac output. In one of Cohn and Steele's experiments, digitalis augmented the cardiac output almost 400 per cent. The action of the drug is manifested by coincidental increase in output, decrease in the pressure in the right auricle, and a diminution in the size of the heart—a triad of phenomena which demonstrates unequivocally that the glucosides have augmented the functional capacity of the heart.

The changes in cardiac output due to the administration of digitalis to animals with experimentally produced cardiac changes have been studied by Cohn and Stewart.[12] In dogs with mitral regurgitation but no heart failure, digitalis had the same effect as in health, *i. e.*, a decrease in minute volume. On the other hand, when Stewart and Cohn[76] produced in dogs auricular fibrillation with consequent enlargement of the heart and decrease in cardiac output, the administration of digitalis resulted in decrease in the size of the heart and increase in cardiac output.

Observations on the effect of digitalis on cardiac output in human heart failure have not been wholly concordant. Using Grollman's original acetylene method, Stewart and Cohn observed increase in the diminished cardiac output of 3 of 4 patients with heart failure and regular rhythm and in all of 3 patients with heart failure and auricular fibrillation. And even in the patient in whom the cardiac output did not rise when digitalis was administered, it fell to a still lower level seventy-two hours later The extensive studies of Friedman, Clark, Resnik and Harrison,[22] in which they used a modification of Grollman's acetylene method better adapted for patients with diminished vital capacity, did not reveal so constant a rise in cardiac output when digitalis is administered to patients with heart failure. Of the 22 patients with heart failure whom they studied, 5 had an increase in cardiac output of more than 10 per cent following digitalization, 4 had a decrease of more than 10 per cent, while the remaining 13 exhibited a change in minute volume of less than 10 per cent. In each of the three groups some of the patients improved, while others did not. Friedman and his associates believe that the difference between their findings and those of Cohn and Stewart is due to the method used by the latter investigators in which the first samples of gas were taken after fifteen seconds; according to Harrison *et al.*, this time is too short to attain a homogeneous mixture in the lung-bag gas system when the vital capacity is diminished (page 37). However, in an extensive investigation using the same method as Friedman *et al.*, Stewart and his associates[78] found increases the output of the failing heart. From these observations, it would appear that when digitalis is administered to a patient with subnormal cardiac output due to heart failure, the cardiac output generally increases. But the abovementioned studies of Friedman *et al.* indicate that this is not invariably the case; a possible rationale for differences in the effect of digitalization on the cardiac output is discussed below (page 702).

Mechanisms of the Changes in Cardiac Output Due to Digitalis.— At first glance, the effects of digitalis on cardiac output appear paradoxical:

1. In health, both in man and the experimental animal, digitalis *decreases* the minute volume of the heart

2. In heart failure, digitalis may greatly *increase* cardiac output, though in other instances it does not affect or even decreases the minute volume.

The mechanism by which digitalis elevates cardiac output in heart failure seems clear enough. The insufficient heart does not empty as completely as in health, the volume and pressure of the blood within the failing chambers during diastole is augmented, and in consequence the systemic veins become engorged. A more than adequate venous return is thus assured and the cardiac output is determined by the functional capacity of the heart. Digitalis increases the functional capacity of the failing heart—through such effects as slowing a rapid ventricular rate, rendering the rhythm of the ventricle more regular in auricular fibrillation, and increasing the force of ventricular systole (see page 694 for details)—and thus elevates the cardiac output.

A more difficult problem, and one which has called forth differences of opinion that have not yet been harmonized, is that of the mechanism or mechanisms by which digitalis diminishes cardiac output in health and in some instances of heart failure. Three possibilities immediately come to mind:

1. That digitalis impairs the contractile power of the healthy, as contrasted with the functionally defective, heart muscle. Such a conception is contrary to the findings on the isolated heart (page 694). Furthermore, it is immediately ruled out of court by the fact that the decrease in cardiac output is accompanied by diminution in the size of the heart, decrease in contractile power would be manifested by dilatation of the heart.

2. That digitalis increases the diastolic tone—using the term in its strict sense (page 305)—with the result that there is greater resistance to diastolic filling with corresponding decrease in cardiac output. But such an increase in diastolic filling would be accompanied by a rise in venous pressure, while such evidence (page 709) as is available bespeaks rather a tendency to fall in venous pressure.

3. That in addition to its cardiac actions, digitalis also has *extracardiac* effects which serve to diminish the venous return to the heart and consequently the cardiac output, a conception which we owe primarily to the investigations of Dock and Tainter.[11] If it could be shown that digitalis diminishes the circulating blood volume, this would explain the phenomena encountered when digitalis acts on the healthy organism, for a decrease in circulating blood volume entails diminution in venous return to the heart, which in turn decreases venous pressure, the size of the heart, and the cardiac output. That digitalis diminishes the size of the heart is indicated by the studies of Harrison and Leonard and Stewart and Cohn (page 697), and that, in health, digitalis diminishes the

circulating blood volume by the observations of Wollheim[60] and Mies.[61]

Dock and Tainter's conception that digitalis diminishes cardiac output by lowering venous return to the heart was based on the observation in dogs that following the administration of the drug there was simultaneous diminution in venous pressure, cardiac size, and cardiac output. Further studies revealed that coincidently the volume of the liver and spleen and the pressure in the portal vein are augmented. Katz and his associates[62] have confirmed these observations in the dog. The increase in the volume of the liver and spleen following digitalization has also been demonstrated in the rabbit by Mies. On the basis of these findings, Dock and Tainter concluded that the diminished venous return to the heart and decrease in circulating blood volume produced by digitalis are due to constriction of the hepatic veins (page 66), as a result of which blood is pooled in the portal region and thus removed from the active circulation. However, it remains to be determined whether constriction of the hepatic veins as a result of digitalis is as important in man as in the dog; other evidence (page 66) indicates that the hepatic throttle mechanism is not as highly developed in man as in the dog and it does not seem probable that constriction of the hepatic veins plays a significant part in the action of digitalis in man. But whatever the mechanism, there would appear to be a good deal of evidence for Dock and Tainter's conception that the diminution in cardiac output produced by digitalis in health is due to diminution in circulating blood volume and consequently venous return to the heart.

In the diminution in circulating blood volume that follows digitalization in heart failure, the action of the drug on the heart is probably also concerned. For increase in circulating blood volume is a result of heart failure, apparently manifesting the engorgement of the stream bed upstream to the failing chamber (page 70). Consequently, when digitalis strengthens the failing heart and thus lessens the engorgement, one would anticipate a fall in the volume of blood in active circulation.

To summarize: Digitalis affects cardiac output through two mechanisms: (1) Through increasing the functional capacity of the heart, which tends to augment cardiac output; and (2) through decreasing the circulating blood volume and venous return, which tends to diminish cardiac output

In health, cardiac output is regulated, not by the functional capacity of the heart but by the venous return (page 31), for the heart is able to pump any volume of blood that is returned to it in the ordinary course of life. The result is that the increase in the functional capacity of the heart due to digitalis does not come into play. On the other hand, the peripheral action of the drug,

which diminishes the circulating blood volume and the venous return, is manifested by decrease in cardiac output.

In heart failure of sufficient severity, on the contrary, the cardiac output is regulated not only by the venous return but also by the functional capacity of the heart. The highest cardiac output is conditioned by the severity of the heart failure, and if the latter is sufficiently pronounced the cardiac output is subnormal even at rest Under these circumstances it is obvious that the increase in the functional capacity of the heart due to digitalis will tend to be manifested by an increment in cardiac output. On the other hand, the diminution in circulating blood volume and venous return also comes into play and tends to diminish cardiac output. Either the cardiac or the peripheral effects of digitalis may predominate in a particular patient—which harmonizes with the finding of Friedman *et al*[22] that digitalization in heart failure may result in either increase or decrease in cardiac output, though the former is more common

THE ELECTROCARDIOGRAM

The administration of digitalis in therapeutic doses often causes changes in the electrocardiogram. Some of these are due to the direct action of the drug on the muscle, others are produced through the intermediacy of vagal stimulation. It is important that the electrocardiographic manifestations of digitalization be borne in mind, for they may simulate myocardial disease, and indeed protracted observation is sometimes needed for differentiation.

The first change in the electrocardiogram due to digitalis is usually the alteration in the *RS–T* interval and *T* wave first observed by Cohn, Fraser and Jamieson[10] in 30 of 34 subjects to whom they administered the drug. Most often this consists in a depression of the *RS–T* interval and a diminution in the height of the *T* wave. Quite characteristic is depression of the *RS–T* interval and only the first part of the *T* wave below the isoelectric level while the terminal portion of the *T* wave rises above the zero level. The diminution in the height of the *T* wave may progress so that it becomes flat or negative. In other cases the *T* deflection is decreased in size or inverted with little change in the *RS–T* interval, while in still others the *RS–T* interval is depressed with little change in the *T* wave. A negative *T* wave may become positive as a result of digitalization. Pardee[11] points out that when axis deviation is present digitalis changes the *T* wave in such a manner that in each lead it becomes opposite in direction to the predominant wave of *Q–R–S* The effect of digitalis on precordial leads has been studied by Strauss and Katz.[59] They observed that the *S–T* segment becomes positive or negative and the *T* wave smaller; in one case the *T* wave disappeared, in another it became negative. The electrocardiograms

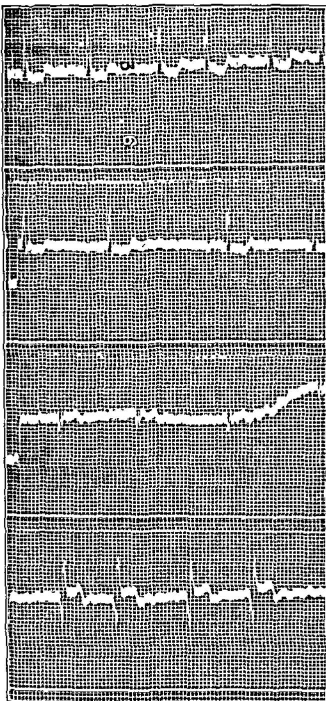


Fig 23 —Effects of digitalis on the electrocardiogram the *RS–T* segment and first part of the *T* wave are depressed in the first and second leads and elevated in the old *fourth lead*

with marked elevation of the *S–T* interval in the fourth lead may closely simulate those of myocardial infarction.

The changes in the *RS–T* interval and *T* wave may be evident within two to four hours after a massive oral dose of digitalis, and

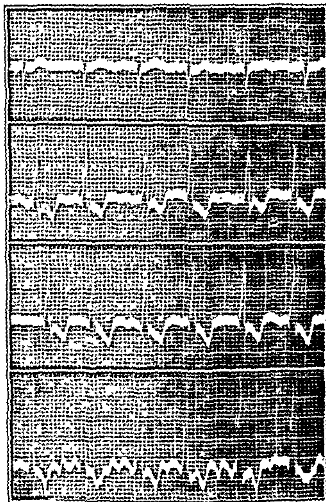


FIG 24.—Effects of digitalis on the electrocardiogram depression of the *RS–T* interval in the second, third and old fourth leads, and inversion of the *T* wave in the second and third leads

may take as long as two or three weeks to disappear. The alterations are apparently due to direct action of the drug on the heart muscle, for they are not abolished by atropinization.

Another electrocardiographic manifestation of the action of digitalis is prolongation of the *P–R* interval. White and Sattler[14]

observed such prolongation in 4 of 5 healthy men to whom they administered 2 to 3 grams of digitalis leaf in the course of seven to ten days. They found that the effects on the *T* wave precede the prolongation of auriculo-ventricular conduction time by several days. In individuals without previous disease of the bundle of His the

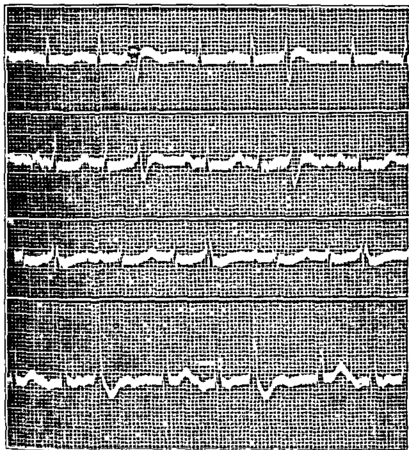


FIG. 25 —Effects of digitalis in the electrocardiogram every third beat is a ventricular extrasystole, resulting in trigeminal rhythm, *P–R* interval longer than previously (old fourth lead).

prolongation of the auriculo-ventricular conduction time by digitalis in the doses used in man is not extreme, rarely exceeding 0.25 second, and according to Pardee does not go on to the degree of block which produces dropped ventricular beats * In individuals with previous

* However, I have recently seen auriculo-ventricular block with dropped beats in a neurotic who treated himself with huge doses of digitalis the block cleared up when the self-medication was discontinued (*cf* also page 724)

impairment of conduction, on the other hand, higher degrees of block may result from digitalis; these will be discussed below in conjunction with the toxic manifestations of digitalization. The lesser grades of impairment of auriculo-ventricular conduction are due largely or entirely to vagal inhibition for they are abolished by atropinization. With higher degrees of digitalis block this is not always the case (Cushny), indicating that here the direct action on the drug on the bundle is significant. It is possible, however, that the atropinization in such observations does not completely abolish vagal inhibition, for in the cat Robinson and Wilson[69] found that after the vagi had been cut the conduction time was unaffected by digitalis given to the lethal dose.

The effects of digitalis on the duration of the individual phases of the electrocardiogram have been studied by Berliner[3] and by Cheer and Dieuaide.[7] They find that the duration of electrical systole, *i. e.*, the *Q–T* interval, is decreased in relation to the complete length of the cycle. It will be recalled that the mechanical tracings also show that digitalis abbreviates systole (page 695), which is prolonged in heart failure Cheer and Dieuaide find that the shortening of systole by digitalis takes place at the same time as the lowering of the *T* wave.

Inversion of the *P* wave or slight slurring or notching of the *Q–R–S* complex are occasionally observed in the course of digitalization (Wedd[83] and Bromer and Blumgart[5]).

The ectopic beats and other changes in rhythm that may result from digitalis are considered on page 724.

The amounts of digitalis required to produce different electrocardiographic changes have been studied on several occasions Robinson and Wilson[69] administered digitalis intravenously to cats and found that inversion of the *T* wave appeared after an average of 23.9 per cent of the fatal dose, definite prolongation of the *P–R* interval after an average of 52.5 per cent, ectopic beats after an average of 71.6 per cent, and complete auriculo-ventricular dissociation by an average of 80 per cent of the lethal dose. Levine and Cunningham[44] found that on intravenous administration about 50 per cent of the fatal dose of digitalis or strophanthin calls forth ectopic beats. However, Gold, Hitzig[29] and their associates point out that these ratios vary with different digitalis preparations

VELOCITY OF BLOOD FLOW

It has already been mentioned (page 58) that digitalization increases the velocity of blood flow in heart failure. Measurement of the circulation time is sometimes useful in following quasi-

quantitatively the improvement of heart failure under treatment. The increased velocity of flow may be definite before subjective improvement is unequivocal.

CIRCULATING BLOOD VOLUME

Wollheim[90] showed that digitalis diminishes the volume of blood in active circulation. Following the intravenous injection of 2 cc. of digipuratum, he observed with the dye method a decrease of between 300 and 1600 cc in the circulating blood volume of 9 normal subjects and 9 compensated and 20 decompensated cardiac patients; in 8 other individuals with heart failure the circulating blood volume was unaffected. Using the carbon monoxide method, Schuermeyer[73] likewise found that digitalization decreases the circulating blood volume in heart failure. With the dye method, Mies[56] found a decrease in circulating blood volume following the injection of strophanthin both in health and in heart failure, the same occurred in rabbits. In the latter, the size of the decrease in blood volume was proportional to the dose of strophanthin, and lasted at least twenty-four hours following a single injection The mechanism of the decrease in circulating blood volume has been discussed above (page 702).

VENOUS PRESSURE

When digitalis is administered to patients with insufficiency of the right side of the heart and is therapeutically successful, the venous pressure falls. I have repeatedly observed a fall in venous pressure following successful digitalization in auricular fibrillation from over 20 cm to about 5 cm within twenty-four hours.

The effect of digitalis on venous pressure in the absence of heart failure is of great interest in conjunction with the mode of action of the drug (page 702). Older animal experiments by Popper[63] and Yohota[92] showed that the venous pressure falls as the arterial tension rises in the early stages of digitalis action. Similarly, Dock and Tainter[15] found a fall in venous pressure in dogs following the administration of digitalis, but their observations were carried out for only a period of two hours or less. In 3 healthy men Stewart and Cohn[77] detected no constant effect of digitalis on venous pressure. On the other hand, on the basis of a more extensive study on 8 *subjects*, Rytand[71] *concluded that digitalis lowers venous pressure* in health. The lowering of venous pressure was most pronounced between twenty-four and thirty-two hours after the administration of digitalis with a return to a normal level between seventy-two and ninety-six hours However, the magnitude of the depression in venous pressure observed by Rytand was so small as to be difficult to evaluate.

ARTERIAL PRESSURE

When large doses of digitalis, far in excess of those used in therapeutics, are administered to animals, the arterial pressure rises. A variety of experiments (see Cushny[13] for details) show that this pressor effect of digitalis is due to arteriolar constriction. With smaller doses there is little effect on the blood pressure, unless the latter is depressed because of heart failure, in which event the arterial pressure rises with improvement of the heart.

In man, a pressor effect is not manifest with the doses of digitalis used therapeutically. This is true not only in the presence of normal blood pressure but also in individuals with hypertension. Indeed, digitalization in heart failure is most often followed by a drop in arterial pressure. The latter is probably not due to any specific action of digitalis on blood pressure, but is rather one of the manifestations of the relief of the cardiac insufficiency. The matter is further discussed on page 82.

MECHANISM OF RELIEF OF HEART FAILURE BY DIGITALIS

It is evident from the foregoing that various mechanisms are concerned in the relief of heart failure by digitalis, and their relative importance varies in different types of cardiac insufficiency. The most important are the following.

1. **Depression of Auriculo-ventricular Conduction.**—In auricular fibrillation, the depression of the conductivity of the bundle of His serves to lessen the number of impulses that the bundle can transmit. The result is that the ventricles are largely shielded from the numerous impulses with which they are bombarded by the auricles, which are undergoing some 500 fibrillary twitches per minute. With the resultant slowing of the ventricles, the diastolic rest period is augmented, the force of the individual systoles increased, and emptying is more complete. A factor of especial importance is doubtless elimination of pulse deficit, *i. e.*, of ventricular systoles which occur so soon after the preceding contraction that they are too feeble to raise the aortic valve and thus represent wasted work.

The efficiency of digitalis in auricular flutter is also partly due to depression of auriculo-ventricular conduction (page 754).

2. **Inhibition of the Sino-auricular Node.**—In heart failure in which the rhythm is regular but the rate rapid, the slowing of the whole heart by vagal inhibition of the sinus (page 695) is undoubtedly often an important factor in improvement due to digitalis. The resultant lengthening of the diastolic rest period is presumably especially favorable when the heart is hypertrophied and dilated. For the thickened fibers of the hypertrophied heart require a longer time for completion of oxygen diffusion and the dilated heart uses more oxygen for the same amount of work.

3 **Direct Action on the Heart Muscle**—This is probably the most important means by which digitalis tends to help heart failure with regular rhythm, but also participates in the action in auricular fibrillation. The direct action on the heart muscle is manifested in several ways which are conducive to the alleviation of heart failure:

(*a*) The absolute force of ventricular systole is increased (page 694).

(*b*) Gremels[31] and Peters and Visscher[62] have found in the heart-lung preparation of the dog that the *efficiency* of contraction of the heart is increased by digitalis bodies in the sense that less oxygen is used for the performance of a given amount of work, in some of Gremels' experiments, the amount of oxygen consumed fell to about one-quarter of the previous quantity when strophanthin was administered. This reduction in oxygen consumption is presumably at least largely a consequence of the diminution in the size of the heart due to digitalis, for Starling and Visscher showed that the oxygen consumption of the heart for the same amount of work becomes greater as the diastolic size of the heart increases.

(*c*) What is doubtless another aspect of the foregoing is that digitalis combats *fatigue* of the heart muscle, which is probably the very essence of most instances of heart failure (page 330). This was illustrated by the experiments of Schaefer[72] on the heart-lung preparation of the cat. He compared the response of digitalized hearts to repeated increments of the venous pressure with rest periods between, and found that the digitalized heart became fatigued more slowly than the control Thus, in one experiment, after four periods of increased venous pressure the digitalized heart still pumped 170 cc. of blood per minute while the minute volume of the control had fallen to about 50 cc.

4. **Decrease in Venous Return.**—The evidence that digitalis decreases circulating blood volume through extracardiac action has been reviewed (page 709) Decrease in circulating blood volume entails diminution in venous return, which reduces the work of the heart and may be a significant factor in bringing the latter within the capacity of the functionally impaired organ Further studies to reveal the quantitative importance of this factor are needed.

Through the mechanisms just enumerated, digitalis increases the heart's capacity for work and perhaps also diminishes the work which the organ must perform Since the manifestations of heart failure result from the work of the heart approaching the functional capacity of the organ—either as a result of increase of the former or decrease of the latter, or more often both—digitalis tends to ameliorate or clear up these symptoms.

A point which is to be emphasized, and which has been brought out with especial force by the important studies of Harrison and

his co-workers (page 701), is that the improvement of cardiac failure by digitalis does not necessarily entail increase in cardiac output, though this usually occurs. This is readily comprehensible in the light of Starling's law of the heart. Let us consider, for example, a patient with left ventricular failure due to hypertension and coronary arteriosclerosis The insufficient left ventricle fails to empty completely; in consequence, as already described (page 300), the chamber dilates, and the volume of blood and pressure within it during diastole increase. The augmented diastolic blood content and pressure within the left ventricle may, as expressed in Starling's law of the heart (page 302), maintain the cardiac output close to its previous level, but at the same time they entail engorgement and hypertension of the pulmonary circuit, which in turn cause dyspnea and other symptoms Digitalis augments the force of the systole of the left ventricle with the result that the chamber empties more completely and the diastolic intraventricular filling and pressure fall. In consequence, the engorgement of the pulmonary circuit is lessened and the resultant dyspnea clears up. What digitalis has done is not necessarily to increase the minute volume of the left ventricle, but to enable this chamber to pump the same volume of blood starting from a smaller diastolic filling. Indeed, the measurements of Harrison and his associates indicate that sometimes the improvement as a result of digitalization is accompanied by decrease in cardiac output, which is perhaps attributable to an extracardiac action of the drug diminishing circulating blood volume and consequently venous return.

THE KIDNEYS AND THE URINE

Withering originally introduced digitalis as a diuretic. Actually, one of the most common evidences of successful digitalization is an increase in the urinary volume accompanied by a loss in body weight. Daily measurements of urinary volume and body weight afford useful indices of the efficacy of digitalis treatment. With successful digitalization of a patient with auricular fibrillation and cardiac edema, the daily urinary volume may rise within twenty-four hours from 200 or 300 cc. to over 3 liters. At the same time the previously typical "cardiac" urine (page 270) becomes light in color, the sediment disappears, the specific gravity falls, albuminuria lessens, and the concentration of chloride rises.

When digitalis is efficacious in failure of the right side of the heart, diuresis always occurs and doubtless corresponds to the resorption of edema, although the latter may be occult and revealed only by loss of body weight. On the other hand, I have several times observed relief of dyspnea and other manifestations of pulmonary engorgement in patients with isolated insufficiency of the left side of the heart without definite increase in urinary volume. In such instances of uncomplicated left-sided failure there is no

edema, other than perhaps pulmonary, and consequently, especially since the fluid intake of the patients is restricted, the urinary output is not notably increased.

The diuretic effect of digitalis is confined to patients with heart failure; in health, nephrotic or nephritic dropsy, the ascites of cirrhosis of the liver, etc., the urinary volume is not increased The augmentation in urinary volume in heart failure is due to improvement of the circulation The resulting fall in venous and consequently capillary pressure and, in some cases, increase in cardiac output, favor the resorption of edema fluid into the blood stream, from which the functionally competent kidney eliminates it There is every reason to believe that it is the resorption of edema which is of primary importance in producing the diuresis, and not the reverse. In accord with this conception, Stewart[75] found that when digitalis is administered to edematous cardiac patients, diuresis is preceded by fall in the specific gravity of the plasma, indicating that diuresis is initiated by mobilization of fluid from the tissues. In addition, in the cases in which digitalis increases the cardiac output, augmented blood flow through the kidney doubtless aids diuresis

Cushny found no evidence of specific action of digitalis on renal blood flow which would tend to favor diuresis In experiments in which he measured the blood flow through the kidneys directly, he found no dilatation of the renal vessels following the injection of doses of strophanthin insufficient to raise the blood pressure; when the latter was raised by large doses, blood flow through the kidneys was lessened by vasoconstriction Likewise, Bartram[2] found that when digitan is injected directly into one renal artery of a dog, the output of this kidney is generally less than that of the other. On the other hand, in experiments on the heart-lung-kidney preparation of the dog, Gremels[32] found evidence that digitalis bodies produce diuresis through specific effect on the renal parenchyma. He observed increase in urinary volume following the administration of strophanthin or digitoxin even though the blood flow through the kidneys was diminished. Gremels believes that the glucosides inhibit tubular resorption of water and chloride. However, it would seem that more evidence is necessary to prove that even part of the diuretic action of digitalis is due to direct action on the kidney.

THE ADMINISTRATION OF DIGITALIS

In the vast majority of instances, digitalis is given by mouth The following remarks concerning preparations and dosage refer to the oral administration of the drug; rectal and parenteral therapy is considered in a subsequent section.

Preparations of Digitalis.—For oral administration, preparations of digitalis are used almost exclusively in this country. Strophanthus, squill, and the other digitalis allies have not been shown to

possess therapeutic advantages over digitalis, and are hardly needed by the practitioner.

An enormous amount of work has been devoted to the identification and isolation of the individual active principles contained in digitalis leaves. It was hoped that some of these principles would possess the therapeutic virtues of the whole digitalis leaf without some or all of the disadvantageous side actions and, since different batches of digitalis leaf may vary in potency, enable more accurate dosage. So far, these hopes have proved illusory. While a number of fractions of digitalis leaf and glucosides are on the market, none of them have proved to have therapeutic advantages over the whole leaf. Moreover, most of these preparations (see *New and Non-official Remedies* for the more important) are expensive, and the cost is often an important consideration in a drug that may be taken for years. It appears that in former years the whole digitalis leaf and its galenical preparations available in many communities were of low and variable potency so that physicians were forced to have recourse to special proprietary digitalis preparations of known merit and relatively constant strength. Nowadays, however, potent digitalis and its galenicals are available almost everywhere. Moreover, the drug as marketed by the leading manufacturers is standardized by biological assay and often further checked by clinical trial. The methods of biological assay most often employed for the standardization of digitalis in this country are the frog method and the cat method of Hatcher and Brody.[11] In the variant of the frog method perhaps most often used, 1 frog unit is defined as the quantity of the drug necessary to produce permanent systolic standstill of the ventricle one hour after injection into the ventral lymph sac. In the cat method, 1 cat unit of digitalis is defined as the minimal lethal dose per kilogram of cat on slow injection into the femoral vein. No two batches of digitalis leaves have exactly the same potency, and for quantitative investigations it is necessary that each be assayed by the cat or some other method. However, most well-dried and undeteriorated digitalis has a strength of about 1 cat unit to 0.1 gram (1.5 grains) of the powdered leaf. Since the official tincture of digitalis is of 10 per cent strength, this means that 1 cc. or 15 minims of the tincture contains 1 cat unit.*

* The statement in the text that 0.1 gram of digitalis leaf or 1 cc. of tincture of digitalis are equivalent to 1 Hatcher-Brody cat unit is based on digitalis standardized according to U.S.P. X. Most of the digitalis turned out by pharmaceutical houses is still standardized in accord with U.S.P. X. However, U.S.P. XI has altered the standardization of digitalis so that the preparations are stronger than those standardized by U.S.P. X. Fahr[15] has pointed out that this has resulted in overdosage by physicians accustomed to the older standardization who unwittingly prescribed digitalis of U.S.P. XI. According to Edmunds,[17] the digitalis of U.S.P. XI is about 25 or 30 per cent stronger than that of U.S.P. X. This means that 1 Hatcher-Brody cat unit is represented by about 75 mg. of digitalis leaf or 0.75 cc. of tincture of digitalis of U.S.P. XI.

The only preparations of digitalis required for oral administration are the powdered leaf, dispensed in the form of pills or capsules, and the tincture. The infusion is more subject to deterioration, presents no advantages, and is now hardly used The pills or capsules permit of accurate dosage and are very convenient for ambulant patients. It is possible that some patients absorb the tincture better, but in at least the large majority of individuals pills or capsules of the powdered leaf are also well absorbed. In using the tincture, it is to be borne in mind that the drop of most medicine droppers is considerably less than 1 minim, with the result that the patient frequently takes much less than the number of minims actually prescribed. However, some firms now dispense tincture of digitalis in a bottle with a dropper that yields 1 minim to the drop.

The Dosage of Digitalis.—Withering[39] advised that foxglove "be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects" His principle of dosage was thus the one recognized as sound today, *i. e.*, that digitalis should be given in quantity sufficient to produce a physiological effect, rather than adherence to arbitrary dosage regardless of whether or not an effect is produced. Subsequently, however, the fear of toxic effects dominated the minds of many clinicians—perhaps largely because of the often unpredictable potency of the preparations at their disposal and vague definition of the field of usefulness of the drug—and inadequate doses of digitalis were often prescribed. With the recognition by Mackenzie[54] of the remarkable efficacy of digitalis in auricular fibrillation, a clinical test object for the dosage of digitalis became available, and it was realized that the amounts previously prescribed were often too small. It is, however, from the careful studies of Eggleston[18] with digitalis preparations carefully assayed by the cat method of Hatcher and Brody that the present conception of adequate digitalis dosage has evolved.

Appropriate dosage of digitalis entails two considerations: (*a*) The initial administration of sufficient of the drug to obtain an optimum therapeutic response with a minimum of undesirable side effects; (*b*) the maintenance of the optimum therapeutic effect over protracted periods.

Initial Dosage.—Formerly, it was the almost universal practice to initiate digitalis therapy with a daily dose that was relatively small, according to present conceptions, but nevertheless exceeded the quantity of the drug excreted or destroyed in the body during the day. By the daily repetition of this dose the amount of digitalis in the body was gradually increased, with the result that an optimum concentration of the drug was usually attained in between three and ten days. The classical example of such gradual dosage

is the practice with which Mackenzie[63] obtained his brilliant results in auricular fibrillation. He started with 1 dram of the tincture (equal to 6 grains of the powdered leaf) daily in doses of 15 or 20 minims When the situation was urgent and the distress great, Mackenzie gave as much as 2 drams daily. These daily rations were continued until adequate slowing of the ventricular rate, a digestive disturbance, or some other toxic manifestation resulted. Then the drug was stopped and the patient carefully observed. When the ventricular rate began to accelerate, digitalis was resumed in doses one-half as large as those initially employed and the subsequent ration decided in accord with the behavior of the patient.

Another procedure for the dosage of digitalis was introduced by Eggleston[18] He found that much larger doses of digitalis than had previously been used can be administered with safety and therapeutic effects obtained in correspondingly less time. Moreover, the massive doses yield excellent therapeutic effects in many cases which are refractory to smaller amounts, and make the parenteral administration of digitalis rarely necessary. By careful observations on a large series of patients, Eggleston found that optimum therapeutic effects are obtained when an average of 0 15 cc. of tincture of digitalis (or 0.015 gram of the powdered leaf) per pound body weight is administered within a period of twenty-four or thirty-six hours Roughly, it may be said that the full therapeutic effect usually requires the administration of about 20 cc. of tincture or 2 grams of powdered leaf to a patient of average weight, with somewhat smaller doses in light people and larger ones in heavy individuals. Eggleston's findings regarding the approximate amount of digitalis necessary for full therapeutic effect and the safety of such large doses have been confirmed by Robinson,[68] Pardee,[69] and others. Of course, it goes without saying that the optimum dose of digitalis, no more than that of any other drug, is not immutably correlated with any one variable such as body weight and doubtless differs for each individual and at different times in the same person. Thus, Pardee found that in different persons the amount of digitalis required to produce the same effects varied from 50 per cent above to 36 per cent below the average. Nevertheless, the dosage recommended by Eggleston represents an approximation which is very valuable in practice as a guide when rapid digitalization is required.

Eggleston advised that from one-half to one-third of the calculated quantity be administered as the initial dose and the rest given in equal fractions at six-hour intervals during the next twenty-four to thirty-six hours For example, in a man weighing 140 pounds, the total amount to be given is about 20 cc. of tincture (or 2 grams of powdered leaf), of which 8 cc. (0.8 gram of the leaf) may be given as the initial dose and followed by six doses of 2 cc. (0.2 gram

of leaf) at four-hour intervals. With these doses, significant therapeutic effects are often evident within six hours after the initial dose and maximum digitalis action may be attained within twelve to eighteen hours. Pardee found that following such large oral doses of digitalis, changes in the *T* wave due to digitalis were present within two hours in 3 of 9 patients and within three hours in 7 of the 9.

It need hardly be cautioned that rapid digitalization using massive doses should not be attempted if the patient has had digitalis in the preceding two weeks. The patient should be under the close supervision of a competent nurse or else seen at frequent intervals by the physician. The nurse should be instructed that if the pulse falls below 70 per minute or coupling appears, or if nausea, vomiting or diarrhea develop, no further digitalis is to be given without first notifying the physician.

Whether rapid or more gradual initiation of digitalization is to be attempted must be decided for the individual patient In general, massive doses of digitalis are to be administered only to patients with severe heart failure and urgent symptoms in whom there is reason to believe that the condition is rapidly becoming aggravated. Especially severe heart failure with a very rapid ventricular rate calls for a large initial dosage to slow the rate as rapidly as possible and thus avert the exhaustion of the heart which a rapid rate favors The majority of those in whom massive digitalization is indicated have auricular fibrillation or flutter. Surgical or obstetrical emergencies, or the development of pneumonia or another acute infection, in a patient with heart failure may call for large doses of digitalis Where the heart failure is but slight or moderate, there would seem to be no advantage in starting digitalization with massive doses The same is true of heart failure of severe degree but considerable standing, in which there is no reason to believe that the condition is rapidly becoming worse. Under these circumstances the administration of digitalis may be started with doses of 2 cc. of the tincture or 0.2 gram of the powdered leaf three times daily.

The Maintenance Dose.—The next problem that arises is that of how much digitalis to give after initiation of the drug by the procedures just outlined. By the initial doses the optimum effect possible under the circumstances has been secured. In some cases the digitalis works so well that the symptoms and signs of heart failure are largely eliminated. In these instances one may proceed directly with the administration of digitalis in doses which serve to maintain the improvement, the so-called maintenance dose In other cases, digitalis meets with little or but moderate success and in the effort to improve this so much of the drug is given that nausea and vomiting, excessive slowing, ectopic beats, or other

manifestations of overdosage appear. Then, it is necessary to pause for a few days until these manifestations clear up and then, if it is decided that digitalis has some prospects of helping the patient, proceed to the administration of the maintenance dose.

The importance of rational maintenance dosage of digitalis is evident from the fact that many patients who have been digitalized must perforce take the drug for the rest of their life, even for a decade or more. In adjusting the maintenance dose, which needs supervision and frequently altering quite as much as does the protracted administration of insulin, two considerations are obviously paramount: (1) That the functional capacity of the heart be kept at as high a level as feasible, and (2) that episodes of overdosage be avoided as much as possible. Actually, many patients who take digitalis for long periods, especially those with auricular fibrillation, become very expert at adjusting the doses of the drug to their needs

The adjustment of the maintenance dose of digitalis is complicated by the facts that: (1) The action of a single dose persists with gradually decreasing intensity for a considerable time; and (2) the action of a second dose during the period of action of the first dose is summated with what is left of the latter. The tenacious persistence of the action of digitalis is illustrated by the effects on the *T* wave, which may still be evident three weeks after the drug is discontinued. Likewise, Robinson[66] found that when the ventricular rate is slowed by a single large dose of digitalis, the effect is still manifest for an average of over nine days It seems a fair assumption, although this is not yet directly proved, that such long-continued action is at least largely due to persistence of the drug within the body.* To some extent, however, protracted improvement of heart failure may be due, in addition to the effect of digitalis remaining in the body, to the interruption by the digitalis of "vicious circles" tending to perpetuate heart failure. Where in the body digitalis is stored is not known. It has been found (see Hatcher and Eggleston[38] and Cushny[13]) that following intravenous administration digitalis disappears from the blood stream within a few minutes. In which organs the glucosides are deposited remains to be discovered; some digitalis has been found in the liver of the rat by Hatcher and Eggleston[38] and of the pigeon by Hanzlik and Wood.[33] But the liver cannot be the sole storage place, for Hatcher and Eggleston found in the rat that strophanthin disappears from the blood stream within two minutes after intravenous

* Recently, Weese[44] and others have found necrotic changes in the heart muscle of animals treated with large doses of digitalis, these lesions appeared several days after the drug had been given. They therefore advance the suggestion that cumulative effects may be due not only to the persistence of the drug within the body but also to alterations induced by the first dose which increase the vulnerability of the animal to succeeding doses More evidence would appear necessary before this view can be accepted. That lesions of the heart muscle are produced in man by digitalis remains to be demonstrated

injection even after the liver is removed. There appears to be no evidence (Cushny[15]) that an especially high proportion of the drug is stored in the heart. Nor is it known to what extent the cessation of action of digitalis is due to the excretion of the drug or its destruction in the body.

Attempts have been made to estimate the amount of digitalis which disappears from the body per day by observing the rate at which some of the manifestations of its action disappear following cessation of the administration of the drug. This was first done by Pardee.[59] He administered digitalis until vomiting appeared. *The drug was then stopped for some days. Digitalis was again* given until vomiting developed. On the assumption that vomiting appears when a fixed concentration of digitalis in the body is exceeded, the difference between the amounts of digitalis given in the first and second courses divided by the number of days that elapse between the courses indicates the average daily rate of disappearance of the drug. By this method Pardee found that on an average 22 minims of tincture (assaying 1 25 cc. per cat unit) disappeared from the body daily. However, in individual cases the daily disappearance of digitalis varied from 55 per cent below to 82 per cent above the average. Similar studies were carried out by Bromer and Blumgart,[4] using changes in the *T* wave and *P–R* interval as the criterion of digitalis action. Their results indicated that the average rate of disappearance of digitalis from the body is 23 5 minims of a tincture standardized to 1 minim per cat unit, the variations were only from 19 8 to 28 9 minims and were not influenced by the weight of the subject, the nature of the cardiac lesion, or the state of compensation.

From these observations the inference has been drawn and widely applied that, once the patient has been digitalized, the amount of digitalis necessary to maintain this state—the maintenance dose—is about 1.5 cc. of the tincture or 0 15 gram of the powdered leaf daily. Such an inference, however, is not justified for, as noted above, Pardee found wide variations in the rate of disappearance of digitalis in different individuals. Likewise, the studies of Gold and De Graff[28] indicate that the daily rate of disappearance of digitalis is by no means constant but is affected by the amount of digitalis in the body and by other factors As would be anticipated, they found that the greater the amount of digitalis in the body the larger is the daily elimination. Presumably such differences in the rate of elimination of digitalis account for Gold and De Graff's finding that a patient may exhibit identical digitalis action—indicating similar effective concentrations of digitalis in the body—from two widely different doses of digitalis each taken for a long time. The available evidence thus indicates that *there is no fixed maintenance dose of digitalis and that the daily ration of digitalis*

necessary to maintain the optimum therapeutic effect varies greatly, not only in different patients but also in the same person at different times. In severe heart failure a higher dose of digitalis is generally required to maintain the optimum effects of the drug, secured by the initial digitalization, than in mild cardiac insufficiency. The findings of Gold and De Graff indicated that "the degree of heart failure determines the 'effective concentration' of digitalis in the body necessary to produce full therapeutic effects and the average ambulatory patient with symptoms of heart failure requires a much lower 'effective concentration' of the drug to attain this result than the average bed-ridden patient with far-advanced congestive failure." In many patients with auricular fibrillation, 0.1 gram daily of the powdered leaf suffices as a maintenance dose to maintain the full therapeutic action of the drug; that this dose actually functions is shown by the fact that when it is discontinued the ventricular rate accelerates and breathlessness develops. On the other hand, in patients with severe heart failure the full therapeutic benefit of digitalis requires the daily administration of 0.4 gram or even more of digitalis and one is unable to avoid recurrent episodes of vomiting, coupling, and other manifestations of overdosage. The maintenance dose of digitalis must be determined for each patient individually and altered to meet changing conditions.

Dosage in Children.—McCulloch and Rupe[50] found that between two and five times as much digitalis per pound body weight is required to produce the effects of the drug in normal children. In children with heart disease they found that the effects of digitalis are qualitatively the same as in adults, but on the basis of body weight an average of twice as much digitalis is required as in adults.

Intravenous Administration of Digitalis.—Because of the relatively prompt action of large doses of digitalis by mouth (page 717), there is rarely occasion for the intravenous administration of digitalis. The rare circumstances in which it is called for include heart failure of such severity that even minutes seem precious, notably patients with acute and massive pulmonary edema in whom morphine and venesection do not suffice to bring prompt improvement, and those in whom gastro-intestinal disturbances prevent the administration by mouth or rectum. In my experience the hope of attaining success by the intravenous administration of digitalis to patients in whom large doses of the drug by mouth have failed to produce improvement has always proved illusory. The intravenous administration of strophanthin is generally preferable to that of digitalis.

For intravenous injection, proprietary preparations available in ampoules are almost always used. For the three preparations, digalen, digifolin solution, and digitan hypodermic solution, Pardee[41] recommends the *slow* injection of 1 minim per pound body weight

in individuals who have not previously had digitalis. Two hours later, if necessary, Pardee advises a dose of 0.25 minim per pound body weight, which may be repeated at intervals of two hours; this smaller dose may also be used in persons who have previously had digitalis. With this dosage, from which he observed no ill-effects, Pardee detected definite slowing of the heart rate within five minutes and marked slowing within fifteen minutes. The writer's experience is confined to an initial dose about one-half that recommended by Pardee, with which he has observed no untoward reactions.

There would seem to be little, if any, need for the subcutaneous or intramuscular injection of digitalis unless one is unable to enter a vein; such injections are often painful.

Rectal Administration.—The rectal administration of digitalis may yield excellent results in patients in whom nausea and vomiting due to heart failure—presumably through the intermediacy of passive congestion of the gastric mucosa—prevent the administration of the drug by mouth. The method has been developed by Levy,[45] who recommends the following technic: The patient is first given a cleansing enema. Then 8 to 20 cc. of digitan is given through a rectal tube. Digitan is an aqueous preparation of digitalis containing the equivalent of 0.1 gram of powdered leaf per cubic centimeter; it is not as irritant as the alcoholic tincture of digitalis However, he was also able to use the tincture, but the latter must be diluted to prevent irritation by the alcohol.

The Intravenous Injection of Strophanthin.—The intravenous injection of strophanthin was introduced by Fraenkel,[21] and is widely used on the continent of Europe Fraenkel and other German clinicians have claimed for strophanthin results in the treatment of heart failure unequaled by other digitalis allies. The method of treatment has not been commonly used in this country, perhaps largely because of the popularization by Eggleston of massive doses of digitalis by mouth, which act rapidly and give much the same results as those claimed by European clinicans for the intravenous injection of strophanthin Moreover, the dose of strophanthin formerly recommended was too large, and resulted in a number of sudden deaths, which led to unjustified fear of the method of treatment.

Strophanthin should not be injected into patients who have had digitalis in the previous ten days. The initial dose should not exceed 0.5 mg. of ouabain (amorphous strophanthin, the preparation containing about 1 cat unit to 0.1 mg.). Using this dose and following it at intervals of one-half hour with smaller injections of 0.1 mg. until a full therapeutic effect (slowing of the ventricular rate to below 80 per minute in patients with auricular fibrillation) was obtained, Wyckoff and Goldring[91] observed no ill-effects in 31

patients. I have used a similar dosage on a number of occasions without observing a dangerous reaction. It would appear that no more than about 1 mg. in twenty-four hours should be administered. In one-half their patients, Wyckoff and Goldring observed slowing of the ventricular rate within five minutes and all who showed any effect did so within fifteen minutes. They found that the action of strophanthin disappeared within five days.

In the few patients in whom intravenous administration of a digitalis ally is required, the use of strophanthin is probably the method of choice. But the advantages of this drug over digitalis by mouth, when the latter can be given, remain to be established It would appear probable, though the writer has no personal experience in this regard, that strophanthin might be valuable in cases of acute pulmonary edema due to left ventricular failure in which digitalis has not been previously administered.

SYMPTOMS OF OVERDOSAGE OF DIGITALIS

The physician must keep constant watch for evidences of overdosage of digitalis, not only when large doses are administered but also, because of the cumulative action of the drug, during the protracted administration of small doses. Some individuals are remarkably sensitive to digitalis and develop toxic manifestations with relatively small amounts. In some patients with severe heart failure, the optimum therapeutic effects are obtained only with a ration of digitalis closely approximating that which calls forth undesirable side effects, so that the latter cannot be avoided on repeated occasions.

It is to be emphasized that, despite the claims made by the sponsors of various proprietary preparations, the toxic side actions of digitalis cannot be avoided by the use of special preparations of digitalis, of the individual glucosides, or of squills, strophanthus or any of the other digitalis allies. The purchase of expensive proprietary digitalis preparations is a waste of money. If the digitalis body in question acts on the heart it will, when present in sufficiently high concentration, produce toxic manifestations. Nor can toxic effects be minimized by the administration of partial doses of different digitalis allies; Hatcher and Brody[16] showed that the digitalis bodies are mutually synergistic, ouabain and the digitalins, for example, summating their effects.

Gastro-intestinal Symptoms.—The most common and usually the initial undesirable manifestations of the action of digitalis are *loss of appetite, nausea and vomiting.* These gastric symptoms usually appear in the order mentioned, and one should warn patients taking digitalis to report anorexia, which may precede vomiting by a day or more. However, sometimes vomiting appears suddenly,

without its precursors; this is especially apt to occur following large single doses. A characteristic of the gastric symptoms of overdigitalization is that they do not appear immediately after the digitalis is taken but after a varying interval. But if the dose of digitalis is very large the period before the onset of nausea and vomiting may be short; following the administration of single doses of 1.5 to 2.5 grams of digitalis, Robinson[68] observed nausea or vomiting in from one-half to one hour after the medication had been taken. Following the stoppage of digitalis the vomiting may last from a single emesis to several days; it may, as Withering pointed out, pass away and recur on several occasions.

There is no constancy about the dose of digitalis which produces gastric symptoms, and individual susceptibilities presumably play a part. Of 100 patients to whom Robinson[68] administered a single dose of 1.5 to 2.5 grams of digitalis, about 10 per cent developed gastric symptoms. Eggleston[21] found that the amount of digitalis producing vomiting varies between 1.25 and 8.5 grams, there was no definite difference in the amount of the drug resulting in vomiting in healthy persons, those with heart disease and regular rhythm, and those with auricular fibrillation.

That digitalis produces vomiting after absorption, and not by direct irritation of the stomach, is immediately suggested by the latent period before the onset of emesis The same is shown by the occurrence of vomiting after intravenous injection. Hatcher and Eggleston[37] observed that animals from whom the gastro-intestinal tract had been removed exhibited evidences of nausea and went through the movements of vomiting after the injection of digitalis bodies. It was therefore thought that digitalis stimulated the vomiting center directly. However, Hatcher and Weiss[39] found that in cats digitalis no longer causes vomiting after the cardiac nerves have been cut They therefore believed that digitalis induces vomiting through its action on the heart, which initiates reflex stimulation of the vomiting center. Subsequently, these findings were controverted by Dresbach and Waddell,[16] who found that the seat of emesis in the cat is not the heart. In the pigeon, also, Hanzlik and Wood[32] find that while digitalis vomiting is of reflex origin, the reflex is not initiated in the heart. It would seem that the mechanism of vomiting due to digitalis requires further investigation.

Diarrhea is an occasional toxic manifestation of the action of digitalis. I recently saw a patient in whom the connection of diarrhea with the administration of digitalis was not recognized because of the absence of other symptoms of intoxication, but the diarrhea cleared up when digitalis was discontinued. Digitalis is especially apt to produce diarrhea in individuals with lesions of the large bowel, *e. g.*, diverticulitis

Cardiac Manifestations.—In addition to the effects on the heart for which digitalis is used in therapeutics, it may produce undesired manifestations. These may appear before the full therapeutic effects of the drug are obtained and force its abandonment.

The most common of the undesirable actions of digitalis on the heart is the production of ectopic beats. Extrasystoles due to digitalis have a remarkable tendency to occur after each regular beat with resultant coupling of the pulse (pulsus bigeminus). The coupling of the pulse often enables the recognition of overdosage in patients with auricular fibrillation, in whom extrasystoles can otherwise be detected only by graphic methods. It is to be borne in mind that exceptionally the extrasystoles are so numerous that overdosage of digitalis is accompanied by acceleration of the pulse despite slowing of the pacemaker. It is generally considered that digitalis produces extrasystoles principally through increasing the irritability of the heart muscle, though doubtless the slowing in rate often favors their appearance. Robinson and Wilson[69] found that when digitalis is administered intravenously to cats premature contractions appear when 75 per cent of the lethal dose has been administered; in similar experiments Levine and Cunningham[44] observed extrasystoles after an average of 52 per cent of the lethal dose. But in man ectopic beats are often seen with a much smaller fraction of a dangerous dose. Indeed, one not uncommonly encounters extrasystoles with very small doses of digitalis in individuals who did not previously exhibit such beats. Interestingly enough, spontaneous ectopic beats are by no means always increased in frequency by digitalis and are not a contraindication to the trial of the drug, indeed, Otto and Gold[57] and others have observed that digitalis sometimes decreases or removes extrasystoles. Recently, in a patient with arteriosclerotic heart disease who had left ventricular failure and numerous ventricular extrasystoles for a period of four months, digitalization produced coincident improvement of the heart failure and disappearance of the extrasystoles.

Excessive slowing of the heart may indicate overdosage of digitalis When the ventricular rate falls below 60 per minute, the drug should be discontinued. The slowing may be due to inhibition of the pacemaker or high-grade auriculo-ventricular block, which on rare occasions has been observed to attain the grade of complete auriculo-ventricular dissociation As already mentioned, it is generally considered that when digitalis in even large therapeutic doses impairs auriculo-ventricular conduction to the degree of producing dropped beats or complete dissociation, the drug is acting on a previously injured bundle.* A rare mechanism by which digitalis slows the heart is sino-auricular block.

* That enormous amounts of digitalis can produce complete auriculo-ventricular block in the healthy human heart is shown by the observation by McGuire and Richards[48] of complete block due to the ingestion of 300 grains of digitalis for suicidal purpose

Mackenzie,[53] Resnik,[65] and others have made observations indicating that digitalis may induce auricular fibrillation; in auricular flutter this often occurs (page 754). In cases of paroxysmal auricular fibrillation it appears that the administration of digitalis may prolong the paroxysm (Fulton[23]) Sinus arrhythmia may result from digitalis: that this is due to vagal stimulation is shown by the disappearance of the arrhythmia under atropine (Cushny[18]). Mackenzie and Windle[53] have observed the production of pulsus alternans by digitalis; this is remarkable inasmuch as spontaneous alternation may be removed by digitalis White[85] has described auricular standstill as a result of digitalis.

In animal experiments large doses of digitalis may produce ventricular fibrillation It is possible that this is the mechanism of the sudden deaths that have been observed following the intravenous administration of strophanthin (Robinson[67]) and perhaps some of those that occur in patients under digitalis treatment. In patients with heart block who were subject to paroxysms of transient *ventricular fibrillation, Schwartz and Jezer*[74] were able to provoke such paroxysms by the administration of digitalis.

The changes in the *R–T* interval and *T* wave and the slight or moderate prolongation of the *P–R* interval that occurs in the course of full digitalization are not to be classed as toxic manifestations.

Other Undesirable Symptoms.—Headache is a common symptom of overdigitalization. Blurring of vision is occasionally encountered. Yellow or green vision is a rare symptom of excessive doses of digitalis. Hallucination, delirium, and various other mental disturbances have been attributed to digitalis intoxication. I have not seen any cases in which the connection seemed clear. It is possible that some of these psychoses were actually manifestations of excessive dehydration; in several cases that I have seen this seemed to have resulted from protracted fluid restriction and salt-poor diet, to which was added not only the diuretic effect of digitalis and salyrgan but also vomiting due to digitalis I have more than once seen improvement in such patients following the cessation of digitalis and salyrgan and the administration of ample fluids and salt.

Eosinophilia has been observed to follow the administration of digitalis, and attributed to vagal stimulation (Romano and Geiger[70]).

THE INDICATIONS FOR DIGITALIZATION AND THE RESULTS OBTAINED

Broadly speaking, the indication for the administration of digitalis is heart failure, *i e.*, a condition in which there is reason to believe that if the functional accomplishment of the heart is augmented the condition of the patient will be improved. However, the results

obtained from digitalis in different forms of heart failure are very unequal.

Significance of the Rhythm of the Heart.—The most striking results are produced by digitalis in cases in which the disturbance of the cardiac mechanism due to auricular fibrillation is *per se* an important element in diminishing the accomplishment of the heart. Spectacular benefit may also be obtained in auricular flutter. In these arrhythmias, the protection of the ventricles from the auricular bombardment may so increase the efficiency of the heart that a patient who sits up gasping for breath and seems at death's door may be sleeping comfortably within a few hours.

The results in auricular fibrillation are so remarkable and so far surpass those in other conditions that some outstanding students (*e. g.* Lewis[46]) of cardiac disease are inclined to limit the administration of digitalis to patients with this arrhythmia and the related auricular flutter. However, such a point of view is unjustified and Christian[8] has rendered great service by combating it. Luten,[43] Marvin,[45] and Gavey and Parkinson[24] have published series of carefully controlled cases, comparing the results on bed rest and fluid restriction alone with those obtained by digitalization, which show conclusively that digitalis may be of value in heart failure without arrhythmia Gavey and Parkinson found digitalis beneficial in 35 of 58 patients with heart failure and regular rhythm; the benefit was pronounced in 18 and slight in 17. It cannot be too strongly emphasized that *many patients with heart failure and regular rhythm are greatly helped by digitalis* Not only is dyspnea often helped but the objective evidences of heart failure may clear up. Excellent objective evidence of the utility of digitalis in patients with regular rhythm is obtained by the measurement of the arm-to-tongue circulation time (page 58). In patients with heart failure and regular rhythm, administration of digitalis is often followed by a quick reduction in the prolonged circulation time. The benefits obtained from digitalis in patients with regular rhythm have seemed to me to be generally greater when the heart rate is accelerated as a manifestation of the failure, and in which the factor of slowing comes into play. Gavey and Parkinson found that digitalis slowed the heart rate in almost half of their patients with heart failure and normal rhythm; the slowing averaged 18 beats per minute in those who were slowed at all. However, I have repeatedly observed great amelioration of dyspnea and other evidences of improvement when the heart rate before the administration of the drug was about 80 per minute. Marvin has pointed out that in patients with regular rhythm digitalis may be beneficial, although there is no significant change in rate.

The use of digitalis in the arrhythmias is considered further in Chapter XXXV.

Significance of the Nature of the Disturbance in Circulatory Dynamics.—Digitalis may be of value in either predominantly left- or right-sided heart failure. The benefits in right-sided failure with systemic venous engorgement—what is commonly known as "congestive" heart failure—are too well known to require further discussion. It may not be amiss, however, to recall that in isolated *failure of the left side of the heart with only pulmonary engorgement*, digitalis may yield splendid results. Harrison, Calhoun and Turley[14] have shown that in this type of circulatory failure digitalis not only ameliorates the exertional and paroxysmal dyspnea but also increases the vital capacity. The improvement is also manifested by diminution in the arm-to-tongue circulation time.

In hypodiastolic heart failure due to compression of the heart by pericardial effusion or constricting pericardial thickening, digitalis, as would be expected, is of no avail. The use of digitalis in the hypodiastolic heart failure of paroxysmal tachycardia is discussed on page 756.

Though the fact is well known, it may be recalled parenthetically that *digitalis is of no avail in the peripheral circulatory failure of shock.* Indeed, the decrease in circulating blood volume produced by digitalis would *indicate that the drug may be harmful in shock.* Nevertheless, digitalis continues to be administered, especially on surgical services, to patients with postoperative collapse and other *obviously peripheral types of circulatory failure—a habit, for such* it usually is—that is to be deplored.

Significance of the Etiology of the Cardiac Changes.—In patients with heart failure and regular rhythm, the results obtained by digitalization are to some extent correlated with the nature of the cardiac lesions. Marvin[55] showed that improvement as a result of digitalization is much more common in arteriosclerotic and hypertensive heart disease than in rheumatic or syphilitic affections, which has also been my experience. On the other hand, this difference is not evident in the cases of Gavey and Parkinson. Within each of these groups, however, the experience of the writer would indicate that to some degree the response to digitalis is conditioned by the mechanism of the heart failure, *i. e.*, to what extent it is due to decrease in the functional capacity of the heart muscle and in what proportion it is a consequence of increase in the work of the heart. Where the latter factor is of at least considerable significance—as in hypertensive heart disease with little or moderate coronary narrowing or in rheumatic valvular lesions in older individuals in whom the activity of the rheumatic inflammatory process in the myocardium is not pronounced—digitalis is likely to be of considerable or even great help. *On the other hand, with florid rheumatic myocarditis,* such as is the rule when the heart fails in young subjects with rheumatic heart disease, digitalis most often is of little or no benefit.

The same is true of diphtheritic and other forms of myocarditis. Why digitalis is usually of little value in syphilitic heart disease, and indeed the entire question of the rapidly downhill course of most cases once failure has set in, remains to be elucidated; implication of the mouths of the coronary arteries is perhaps one important factor.

In heart failure with *auricular fibrillation*, Gavey and Parkinson observed much better results in the cases of rheumatic etiology than in those due to hypertension and arteriosclerosis; this has also been my experience.

In the *emphysema heart*, digitalis is occasionally beneficial, but more often is of no value unless there is auricular fibrillation. It is to be remembered that the breathlessness of these patients is due not only to heart failure but usually in greater degree to the pulmonary changes, and the latter are not affected by digitalis.

In *thyrotoxic heart failure*, likewise, digitalis alone rarely helps. The acceleration in rate is not at all or but little a manifestation of heart failure and usually is little affected by digitalization. Indeed, sometimes the thyrotoxic origin of auricular fibrillation is first suggested by the failure of digitalis to slow the pulse (page 789).

The use of digitalis in the heart failure of *hypertension* was formerly regarded as injudicious because of the fact that digitalis raises the blood pressure in animal experiments. But this does not occur in human beings (page 710), and it has seemed to the writer that excellent results from digitalis in patients with regular rhythm are most often obtained when hypertension is the primary factor in causing heart failure.

In the *myxedema heart* and cardiac failure of *avitaminosis* (beriberi heart), digitalis appears to be useless.

The use of digitalis in *coronary thrombosis* is discussed on page 781.

Influence of Valvular Defects.—In patients with valvular defects it has been thought that digitalis is of much more value in mitral than in aortic lesions. The hypothetical explanation was advanced that the slowing due to digitalis augments aortic regurgitation as a result of the prolongation of diastole. However, it would appear that the difference in the accomplishment of digitalis is at least largely, if not entirely due to the fact that heart failure in mitral disease is much more often due to auricular fibrillation, which responds so well to digitalis. Furthermore, a considerable proportion of the aortic cases are of syphilitic etiology; their usually intractable nature has already been mentioned. I have repeatedly seen benefit from the use of digitalis in rheumatic aortic regurgitation and stenosis, and less often in luetic aortic regurgitation.

Digitalis in Patients With Angina Pectoris.—Caution has been advised in the use of digitalis for heart failure due to coronary

arteriosclerosis with anginal pain. Gilbert and Fenn[25] and others have published cases in which the administration of digitalis was followed by the appearance or intensification of cardiac pain. Contrariwise, in an investigation on 120 patients with cardiac pain due to arteriosclerotic heart disease, Gold, Otto, Kwit and Satchwell[30] arrived at the conclusion that "in cases of angina pectoris without congestion the likelihood is negligible that the use of digitalis will, by a direct action on the circulation, increase or diminish cardiac pain." I have, however, repeatedly encountered patients with coronary disease or hypertension, in whom cardiac pain was aggravated or even initiated while taking digitalis; while exceptional, they are not rare. Gilbert and Fenn attributed the pain to coronary constriction. However, the effect of digitalis on coronary flow is apparently complex and not yet entirely clear. It is a common observation that when patients with coronary arteriosclerosis or aortic regurgitation and angina pectoris develop failure of the right side of the heart, the cardiac pain lessens or disappears. It is therefore possible that the development of anginal pain after the administration of digitalis is correlated with the increase in the functional capacity of the heart (see page 421 for further discussion of the mechanisms involved), and is not due to coronary constriction. In any event, digitalis is often of great value in the failure of the arteriosclerotic heart and worthy of a trial in at least the large majority of instances, for it is only the exceptional patient who develops pain.

Digitalis as a Prophylactic of Heart Failure.—Recently, Christian has advocated that digitalis be used not only in actual heart failure, but also in individuals without heart failure but having such conditions as valvular defects, hypertension, etc , which strain the heart, entail cardiac hypertrophy, and sooner or later lead to cardiac insufficiency. There is good evidence (Chapter XVIII) that hypertrophy evolves from antecedent dilatation, and if the administration of digitalis, by increasing the functional capacity of the heart muscle, would lessen dilatation, it is to be presumed that hypertrophy would be less massive. Christian cites experiments by Cloetta in which he observed that animals receiving digitalis had lighter hearts than controls, and that animals with experimental aortic regurgitation which were given digitalis had smaller and more efficient hearts than those which did not receive the drug. Christian's conception that the administration of digitalis in conditions of cardiac strain may serve to defer the onset of heart failure would seem worthy of further study. But pending the acquisition of facts to support the theory, it does not appear warranted to administer digitalis for long years to individuals with cardiac lesions but no evidences of heart failure

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CHAPTER XXXV

THE TREATMENT OF HEART FAILURE: III. DIURETICS, PARACENTESIS, OXYGEN, PHLEBOTOMY, AND THYROIDECTOMY

DIURETICS

Utility of Mercurial Diuretics in Heart Failure.—Since the introduction of the powerful mercurials, diuretics have come to play a much more important rôle in the treatment of heart failure than previously. Not only do they supplement digitalis, but instances are not rare in which mercurials are decidedly more efficacious than digitalis. Especially is it to be emphasized that the sphere of usefulness of the mercurial diuretics is by no means limited to patients with palpable edema; they often yield splendid results in individuals in whom physical signs of dropsy are lacking but water retention is demonstrated by the large loss of weight that follows the administration of a diuretic.

Following successful mercurial diuresis in heart failure, the patient often feels greatly relieved. Continuous dyspnea is ameliorated and attacks of cardiac asthma may be rendered less frequent and severe or abolished. The abdominal discomfort due to engorgement of the liver and perhaps of the portal tributaries is often notably improved. Objectively, not only is subcutaneous edema lessened and effusions into the serous cavities diminished in volume, but the swollen neck veins and liver shrink and the râles of pulmonary engorgement disappear. Friedman, Resnik, Calhoun and Harrison[19] have found that successful diuresis due to salyrgan or theophyllin often results in increase in vital capacity. In their observations diuresis was associated with increase in cardiac output in 3 patients, decrease in 1, and no change in 8. They believe that this variable effect on cardiac output is due to the simultaneous operation of two mechanisms: (1) Decrease in peripheral edema which diminishes the volume of blood flow needed by the tissues as a result of more efficient metabolic exchanges between the blood and tissues when the latter are not water logged; and (2) decrease in edema of the heart itself which augments its functional capacity and consequently the cardiac output.

Indications for the Mercurial Diuretics in Heart Failure.—The chief use of the mercurial diuretics in heart failure is to augment the improvement obtained by rest, fluid and salt restriction, and the administration of digitalis. In cases with auricular fibrillation in which digitalis alone rapidly restores compensation and com-

pletely alleviates water retention, the mercurials are not required. But there are also many instances of auricular fibrillation in which the improvement obtained by digitalis is not complete, and then the mercurials may be very helpful. However, the mercurials find their chief usefulness in cases with regular rhythm, in which the limitations of digitalis are far greater than in fibrillation of the auricles. Excellent diuresis may be obtained in both arteriosclerotic and rheumatic heart disease, although there is difference of opinion as to which group yields the better results. Marvin[27] found that diuretics are much more often of help in arteriosclerotic and hypertensive heart disease, while Goldring[21] found that 80 per cent of his patients with rheumatic heart disease reacted to mercurials, as contrasted with only 37 per cent of his arteriosclerotic subjects. Other conditions being the same, I have not noticed any difference in the reactivity to mercurials of the different etiological forms of heart failure. Abundant diuresis is sometimes produced by mercurials in the presence of active rheumatic carditis, a condition in which digitalis is only too often ineffective. The most profuse diuresis generally results from mercurials when right heart failure has produced swelling of the veins, peripheral edema, and a large liver. But splendid results are often also obtained in isolated failure of the left side of the heart with solely pulmonary engorgement. In left-sided failure both paroxysmal and continuous dyspnea may be greatly ameliorated; often, a weekly injection of a mercurial prevents previously frequent attacks of cardiac asthma. The effect on dyspnea in these cases of left-sided failure is probably largely a result of diminution in pulmonary edema, even though the latter is clinically occult. In some cases of constrictive pericarditis, mercurial diuretics greatly diminish edema, ascites, and swelling of the liver, although in others they fail abjectly; of course, the improvement is purely temporary. In deeply cyanotic patients with right heart failure secondary to pulmonary disease, I have seen little utility from mercurials. In the first days of coronary thrombosis, when shock dominates the clinical picture, mercurials do not seem indicated; in fact, I twice saw collapse following the injection. But in the subsequent course of myocardial infarction with heart failure, the mercurials may be very helpful.

The most frequent contraindication to the use of the mercurials is impairment of renal function. Especially in elderly patients with hypertension and arteriosclerosis, one should make sure of the state of the kidneys before injecting mercurials. If the urine is dark in color and the specific gravity exceeds 1.020, either spontaneously or in the concentration test, renal function is not seriously impaired and there need be no fear of administering a mercurial. When the specific gravity of the urine exceeds 1 020, one need not determine the non-protein nitrogen of the blood before injecting a mercurial,

for any increase which may be present is not due primarily to impairment of renal function (except in acute glomerular nephritis) If the maximum specific gravity of the urine in the concentration test is only about 1.015, mercurials should be given cautiously and at intervals of at least a week. When the specific gravity is fixed about 1.010, even though the non-protein nitrogen of the blood is not elevated, mercurials should not be injected for there is considerable danger of retention and toxic manifestations. Nor should mercurials be given in the presence of active glomerulo-nephritis with red blood cells in the urine; they increase the hematuria and doubtless damage the kidneys On the other hand, even massive albuminuria is not a contraindication to the mercurials; as long as renal function is not seriously impaired they may be given without fear when chronic passive congestion of the kidneys has resulted in copious albuminuria Mercurials should not be administered to patients who are almost moribund; I have seen them add the *coup de grâce* by producing anuria.

If care is taken not to administer the mercurials to individuals with impaired renal function, undesirable side effects are rare. They include colitis, stomatitis, fever, increase in albuminuria, hematuria, oliguria, and collapse In 30 necropsies on individuals who had received mercurials for long periods, Tarr and Jacobson[27] detected evidences of mercurial damage to the kidneys in only 1. But instances of tubular necrosis due to mercurial diuretics have been reported by others. Local tissue damage and excessive dehydration will be mentioned below.

Administration of Mercurial Diuretics in Heart Failure.—The mercurial diuretics most widely used in this country are mercupurin and mersalyl (salyrgan) In mercupurin the organic mercurial is combined with about five per cent of theophyllin. The combination of theophyllin with the mercurial appears to augment the diuretic potency (*cf.* Hayman[22]) and De Graff[15] and his collaborators have found the addition of theophyllin accelerates reabsorption from the tissues and lessens local injury. Mercupurin would therefore appear to be the more advantageous diuretic.

Even when renal function is good, one should administer mercurials with circumspection. A test dose of 0.5 cc. of either mercupurin or mersalyl (salyrgan) should first be given intravenously or intramuscularly. If there are no ill-effects, this may be followed by 2 cc. in one or two days Larger doses, such as 4 cc., have been used and have produced diuresis where smaller amounts were ineffective, but, for fear of untoward reactions, the writer has no experience with them. In many patients the mercurials are effective and produce no pain (especially mercupurin) when injected deep into the buttocks. But if they cause immediate pain or subsequent indurations, or are not effective intramuscularly, they should be given intravenously

Great care is to be taken to avoid paravenous injection, which produces severe sloughs. Intravenous injection is sometimes successful after the intramuscular route has produced little diuresis. Intraperitoneal injection has been recommended in patients with ascites as producing diuresis of longer duration, but the writer has seen severe peritoneal reaction from this procedure. The injections may be repeated at intervals of from four days to a week or longer. While more frequent injections have been used, this would seem to be tempting untoward reactions for doubtful advantage The diuresis usually starts within three hours and is most often complete within the day, although it may be protracted for forty-eight hours. Because the diuresis is generally at its height within a few hours, it is well to give the injection in the morning so that the patient's sleep is not disturbed by the necessity to void.

Recently, rectal suppositories of organic mercurials have been introduced. They often produce diuresis equal to that obtained by injection, and I have found them very useful Their use is sometimes prevented by *rectal irritation. De Graff, Cowett and Batterman*[16] have found that severe rectal irritation is much more likely to occur with Salyrgan than with Mercurin suppositories, for which reason the Mercurin variety should be used

Keith, Barrier and Whelan[24] pointed out that the effect of the mercurial diuretics may be greatly enhanced by the preliminary administration of salts which produce acidosis In some patients in whom a mercurial alone is ineffective, it produces abundant diuresis after salts entailing acidosis have been given Of these, the most widely used have been ammonium chloride, ammonium nitrate, and calcium chloride. In the experience of the writer, ammonium chloride has been the most effective. Six to 9 grams daily may be given for two days before and on the day of the injection. Smaller doses are less effectual, for the ability of the salt to favor diuresis apparently depends at least preponderantly on the acidosis produced. Ammonium chloride should be given after meals, either in enteric coated capsules or in orange juice or other fluid. Unfortunately, ammonium chloride frequently causes anorexia, nausea and vomiting, and less often diarrhea, which not rarely force its discontinuance. For this reason, it does not seem wise to give ammonium chloride if mercupurin alone produces abundant diuresis

Another factor which may influence the diuresis produced by the mercurials is the chloride content of the blood. In 2 patients, Goldring[21] observed that while the chloride level in the plasma was low salyrgan produced no diuresis, but did so after the administration of 5 grams of sodium chloride daily for three days.

Some patients are kept free of edema and symptomatically improved for long periods of time, even years, by injections of

mercurial diuretics. Indeed, especially in hypertensive and arteriosclerotic heart failure, the use of the mercurials may mean the difference between being bed-ridden and up and about for at least part of the time. Scherf[35] mentions a patient who had 600 injections over a period of twelve years. But more often the efficiency of the diuretic becomes less and less as time goes on and the condition of the patient becomes worse. Goldring[21] found that the response to diuretics is of prognostic significance; of 25 patients who responded to diuretics, 15 were able to leave the hospital in an improved state; while of 21 in whom diuretics were unsuccessful, only 6 left the hospital alive and all were in a precarious condition

Dehydration and Salt Privation Due to Mercurial Diuretics.—The very success of mercurial diuresis may lead to untoward effects (*cf.* Poll and Stern[30]). Following an abundant diuresis, the patient often feels weak for a day or two. This is doubtless due to the rapid removal of large quantities of water and sodium chloride from the body, for it occurs only when the urinary volume is large. More important is a state which develops, usually in older patients with arteriosclerotic heart disease, after repeated and successful use of mercurials with protracted salt and water restriction and usually digitalis—the latter measures have often been carried out for years As a result of all these procedures, not only is the edema removed but the patient becomes dehydrated with a dry and inelastic skin. While the evidences of heart failure are greatly improved as a result of the treatment, actually the patient is worse. A state of weakness, apathy and anorexia sets in, and not rarely this is followed by mental disturbances including delirium and hallucinations. The mental syndrome may progress to coma. Most of the so-called cardiac psychoses that I have seen in the past few years have been of this nature, accompanying dehydration following the protracted use of the mercurials. Presumably, the picture is due to the removal of excessive amounts of water and sodium chloride from the body. Most often there is hypochloremia, but sometimes the chloride content of the plasma is normal or even a little high despite obvious severe dehydration of the tissues as revealed by the skin and tongue. I have made no observations on the sodium content of the plasma. There is often azotemia, presumably due to decreased blood flow through the kidneys. The therapy consists in the administration of abundant fluids and sodium chloride. With this treatment, most, but not all, of the patients improve. It may take several weeks until the mental state returns to normal.

Diuretics Other Than the Mercurials.—The mercurials are so often effective that other diuretics are being used less and less This is especially true of the formerly popular xanthin derivatives. Theobromine (0.5 gram, three times daily) and theobromine sodiosalicylate (diuretin, 1 gram, three times daily) sometimes produce

diuresis in cardiac edema but often fail. Theophyllin (theocin, 0.3 gram, three times daily) is a more powerful diuretic and more often successful in cardiac failure. All of these xanthin derivatives, especially theophyllin, are apt to produce gastric disturbances when given in adequate doses, and should be administered for only three days at a time.

In recent years, urea has been used considerably as a diuretic in heart failure, especially when edema persists over long periods despite digitalization. To be effective, urea must be given in doses of 50 to 100 grams daily. In this dosage, urea sooner or later causes gastric disturbances in many patients, which force its discontinuance. Individuals with heart failure are less likely to tolerate urea for long periods than those with nephrotic edema, perhaps because of chronic passive congestion of the gastric mucosa. Urea may also cause diarrhea. Another deficiency of urea is that the increase in urinary volume is usually accompanied by little augmentation in salt output. This perhaps accounts for the frequent observation that patients taking urea do not lose as much edema and weight as might be anticipated from the increase in urinary volume; they often become very thirsty and lose less water by extrarenal paths

Ammonium chloride, calcium chloride, and other salts producing acidosis have been of little avail in my experience in the treatment of cardiac edema other than as adjuvants to mercurials (page 735) As independent diuretics, the dose is about 9 to 12 grams daily, an amount that may produce gastric disturbances and often results in but little diuresis. I have discontinued the use of these salts as independent diuretics.

Calomel, incorporated with digitalis and squill in the famous Guy's Hospital or Addison's pill for cardiac dropsy, is hardly needed now that the far more efficient organic mercurials are available

MECHANICAL REMOVAL OF EFFUSIONS

Patients with heart failure are often greatly aided by mechanical removal of effusions. Pleural transudates come into question most often. Even moderate pleural effusions augment dyspnea in the presence of heart failure, and they should be tapped when of much smaller volume than would be considered an indication in, for example, tuberculous pleurisy. Because of the instances, excessively rare though they are, in which acute pulmonary edema follows the tapping of a pleural effusion, not more than 1500 cc. should be removed at a sitting. Especially in cardiac patients, one should discontinue the paracentesis if there is augmentation of dyspnea, cough, or expectoration. The removal of as little as 500 cc. from the pleura, especially from the left side, may result in notable amelioration of dyspnea, and I have observed definite fall in venous

pressure following tapping of this volume. One manifestation of the favorable effect of removal of a pleural transudate is sometimes the subsequently more effective action of digitalis and diuretics. If massive ascites accumulates and does not respond to digitalis and diuretics, it should be tapped. Since the introduction of the mercurial diuretics, drainage of subcutaneous edema by means of Southey's tubes or multiple incisions is very rarely called for. On these rare occasions, however, large amounts of fluid may be drained, with temporary amelioration of the condition of the patient, who, not having responded to diuretics, is usually close to the end of his sufferings. The danger of infection during the drainage of subcutaneous edema is much less in cardiac than in neprotic dropsy.

Pericardial effusion large enough to warrant tapping is almost always an exudate, most often of tuberculous or rheumatic origin. On rare occasions, purulent pericardial effusion produces symptoms of circulatory failure so urgent that paracentesis must be performed prior to the surgical drainage of the cavity. Purulent pericardial effusion may accumulate with remarkable rapidity so that the circulatory failure attains ominous severity within a few hours Hemopericardium may also produce an emergency. A man with Gaucher's disease became violently dyspneic during ward rounds and seemed to be expiring; examination revealed signs of pericardial effusion, and the removal of 1500 cc. of blood by paracentesis was life saving. In contrast to these emergencies, it is to be emphasized that the large majority of rheumatic pericardial effusions, and many of those of tuberculous etiology, need not be tapped. They do not produce symptoms of cardiac compression, evidently because they form so slowly that the pericardial sac has time to stretch, and in the course of time most of them resorb spontaneously. The more frequent taking of roentgen pictures has shown that pericardial effusion which produces no symptom or definitely diagnostic physical sign is much more common in rheumatic carditis than was formerly realized, and most often resorbs spontaneously. Paracentesis should be performed only in the exceptional cases in which there is definite evidence that the effusion is hampering the circulation. The most frequent such evidence is the intensification of dyspnea and especially the development of orthopnea in a patient with physical signs or roentgen evidence of pericardial effusion Deepening of cyanosis may also testify to the circulatory embarrassment caused by the effusion. Sometimes, the first evidence that a pericardial effusion is hampering the filling of the heart is swelling of the cervical veins and rise in venous pressure. It should be remembered that palpability of the left lobe of the liver is not necessarily a sign of circulatory failure in an individual with a pericardial effusion; it may be due to the downward displacement of the liver by the accumulation of the fluid in the lower part of the pericardial

sac and to compression of the hepatic veins by the pericardial exudate (page 602). Fall in arterial pressure is an indication for paracentesis of the pericardium.

Various routes have been advocated for paracentesis of the pericardium. In the one most frequently used, the puncture is made 1 or 2 cm. mesial to the lower portion of the left border of cardiac dulness and lateral to and below the apex impulse, when the latter can be felt. Here, the subjacent portion of the heart is the thick-walled left ventricle and if the needle perforates it a little, which may be unavoidable, little harm is done apart from the very rare eventuality of tearing a large coronary branch In other cases the fluid is most readily reached by tapping posteriorly, under the angle of the left scapula. This is especially apt to be true when the presence of a large area of flatness posteriorly (Ewart's sign) indicates that the distended pericardial sac bulges far posteriorly According to Connor,[13] the sac then extends between the spine and the left lung, displacing the latter toward the axilla. Connor, to whose excellent article the reader is referred, believes that when feasible the posterior tap is simplest and safest, and this coincides with the writer's experience In both the methods just described, the needle passes through the pleural cavity For this reason, they are best avoided in tapping effusions believed to be purulent, as in pneumonia and pyogenic sepsis In such cases, Connor recommends that the tap be attempted by Larrey's method, which avoids the pleura In this method, the needle is inserted as high as possible in the notch between the ensiform and the left costal margin and directed slightly upward, sharply backward, and to the left.

OXYGEN

The inhalation of high concentrations of oxygen is a measure that has been increasingly applied of late years in the treatment of heart failure. Beddard and Pembrey[6] long ago showed that when patients with heart failure breathe an atmosphere rich in oxygen the minute volume of ventilation diminishes and dyspnea is ameliorated. The effects of oxygen therapy in cardiac insufficiency have been studied in detail by Barach and Woodwell[5] and Barach and Richards[4] They found that in cardiac patients with diminished oxygen saturation of the arterial blood, the respiration of an atmosphere enriched in oxygen elevates the oxygen saturation of the arterial blood to normal. And if the carbon dioxide content of the arterial blood was previously depressed as a result of hyperventilation (page 132), this also rises. Barach and his associates further found that in some patients with heart failure oxygen therapy results, in addition to the relief of dyspnea and cyanosis, in slowing

of the pulse, diuresis, diminution in edema, and fall in the elevated lactic acid content of the blood.

The primary indication for oxygen in heart failure occurs in the cases in which there is deficient oxygen saturation of the *arterial* blood. As seen in Chapter VII, arterial anoxemia is present in only some patients with heart failure, namely, those in whom the changes in the lungs due to chronic passive congestion or such complications as pulmonary edema, infarction, or bronchopneumonia have hampered the gas exchange between the blood and the alveoli. In such cases, the administration of oxygen generally relieves cyanosis and often, although not always, ameliorates dyspnea. In addition, the elimination of the arterial anoxemia doubtless has further favorable effects on organs which have suffered from deficient oxygen delivery. The effect on the heart itself may well be important in some cases, for anoxemia is deleterious to the function of the myocardium. In experiments on the dog, Resnik[31] showed that arterial anoxemia produces, after an initial stage of enhanced conductivity, depression of auriculo-ventricular conduction. He also found that ventricular fibrillation is prone to develop during anoxemia. In humans, Barach and Woodwell observed that bundle-branch block may diminish in degree following the inhalation of oxygen, and Baker[1] published an instance of transient bundle-branch block which cleared up during the administration of oxygen.

While arterial anoxemia remains the prime indication for oxygen therapy in circulatory failure, the recent introduction of an easy technic for administering close to 100 per cent oxygen (*cf.* Boothby, Mayo and Lovelace[10]) has broadened the sphere of usefulness of this method of therapy. By the administration of 100 per cent oxygen, it is possible to increase the amount of oxygen in the arterial blood from the normal of about 19.5 cc. to about 22.2 cc. per 100 cc. blood (Boothby *et al.*). This increase in the oxygen content of the blood results in delivery of oxygen to the tissues under correspondingly increased pressure. Boothby and his associates and Barach[2] point out that this increase in the pressure under which oxygen is delivered to the tissues tends to alleviate the anoxia which results, despite normal oxygen saturation of the arterial blood, from the deficient blood flow of peripheral circulatory failure. One hundred per cent oxygen has thus proved of considerable value in various forms of shock. It has also proved of great help in pulmonary embolism and in coronary thrombosis, and sometimes relieves anginal pain. Barach found that inhalation of 100 per cent oxygen produces irritative changes in the lungs of experimental animals after two to four days. For this reason, Barach advises that 100 per cent oxygen should not be administered for more than two days continuously,

or else for twelve hours of each day with inhalation of 50 to 60 per cent oxygen in the intervals.

The principal utility of oxygen treatment in heart failure is in four groups of patients:

1. Those with arteriosclerotic, rheumatic, or syphilitic heart disease in whom insufficiency of the left side of the heart has resulted in pulmonary changes sufficient to produce marked cyanosis. Oxygen is especially apt to be valuable where there are such complications as pulmonary edema, infarction, or bronchopneumonia, or where heart disease even without failure is complicated by lobar pneumonia. In acute pulmonary edema, the administration of oxygen may be life-saving.

2. In emphysema or other primary pulmonary disease with secondary heart failure. Such patients are generally deeply cyanotic, and an oxygen-rich atmosphere is often of great help

3. In coronary thrombosis (page 778).

4. In shock (page 805).

In all these varieties of cases the value of oxygen differs greatly in individual patients (Hamburger *et al*[22]). Sometimes it clears up the cyanosis without notable effect on the dyspnea or other symptoms. Very often, while both cyanosis and dyspnea are helped, the heart failure progresses But there are also cases in which all the manifestations of heart failure are definitely helped by oxygen therapy. Some such patients, notably those with pulmonary disease and secondary heart failure, must be given oxygen for weeks at a time; they become intensely cyanotic and dyspneic and the pulse becomes very rapid when the oxygen is discontinued.

Recently, Barach and Martin[3] have found that the *inhalation of oxygen or air under positive pressure* of 5 to 8 mm.Hg may clear up pulmonary edema due to heart failure. Apparently, the induction of positive pressure within the chest lessens transudation both as a result of directly opposing intracapillary blood pressure and as a consequence of the diminution in pulmonary engorgement due to the impediment to the filling of the right heart Detailed clinical observations with this ingenious measure are to be awaited.

PHLEBOTOMY

Removal of blood from a vein often affords relief to patients with intense passive congestion due to heart failure. Successful venesection may be promptly followed by relief of dyspnea and orthopnea, diminution in cyanosis, fall in venous pressure, and decrease in the size of the liver. While the needle was still in the vein, I have repeatedly seen the venous pressure fall 10 or more centimeters. Brams and Golden[12] found that the drop is most marked when venous hypertension is present; while a partial return

toward the previous level occurred within a few minutes, the venous pressure was still between 12 and 78 per cent below this level one hour after the phlebotomy. It is to be emphasized that venesection is of value not only when there is systemic venous engorgement; the drawing of blood may yield splendid results in isolated left heart failure with pulmonary but no systemic venous engorgement Although the blood is then removed from an antecubital vein which is not engorged, the effect is to lessen the pulmonary engorgement; this may be demonstrated radiographically by clearing of previously clouded lung fields

Venesection is probably most often beneficial in left ventricular failure with intense pulmonary engorgement, especially when this is secondary to hypertension and coronary sclerosis in individuals of plethoric habitus with a high circulating blood volume. In such patients dyspnea and orthopnea may be relieved and cyanosis lessened while the needle is still in the vein during the course of a venesection of from 400 to 1000 cc. In acute left ventricular failure with pulmonary edema, venesection sometimes seems life-saving. The same is true in some paroxysms of cardiac asthma in which morphine does not suffice. In primarily right-sided failure due to emphysema or other chronic pulmonary disease, venesection reduces the venous engorgement, but in my experience the relief of subjective symptoms has not been as evident as in pulmonary engorgement. The experiments of Fineberg and Wiggers[13] indicate that vensection may actually be harmful in primary right-sided failure, for through lowering the initial filling of the right ventricle it tends to handicap this chamber in overcoming increased resistance in the pulmonary circuit. It would thus appear that venesection is contraindicated when acute right ventricular failure results from pulmonary embolism.

The amount of blood removed varies between 300 and 1200 cc., depending on the response and the condition of the patient. From plethoric hypertensive patients of sthenic habitus, large amounts are taken, smaller from asthenic individuals Needless to say, venesection should rarely be performed when anemia is present.

The mode of action of venesection in heart failure is not altogether clear. The immediate relief of dyspnea and other symptoms, when it occurs, is plausibly explained by the diminution in the blood content of engorged portions of the circulation, notably the lungs. However, it is questionable whether the more lasting improvement sometimes obtained is to be explained entirely on the basis of decrease in circulating blood volume. In the healthy animal, it is known that following the removal of blood the circulating blood volume is restored within a matter of minutes by mobilization of blood from the reservoirs and inflow of fluid from the tissue spaces, and it is to be presumed, although not yet demonstrated,

that similar restoration of blood volume occurs rapidly in heart failure. Experimental evidence shows that decrease in blood volume entails diminution in the size of the heart, and it is possible that reduction in dilatation following venesection may improve the efficiency of the heart for a period outlasting the decrease in blood volume. Resnik, Friedman and Harrison[22] found that following venesection in heart failure, presumably as a result of lessened pulmonary engorgement with resultant decrease in the work of the muscles of respiration, the oxygen consumption and the cardiac output are usually diminished. The consequent decrease in the work of the heart may also be advantageous. That the diminution in the viscosity of the blood which results from dilution with tissue fluid is significant in lessening the work of the heart does not seem likely.

THYROIDECTOMY

Rationale.—An innovation of the past few years in the treatment of heart failure and angina pectoris is the introduction of total ablation of the thyroid gland by Blumgart, Levine and Berlin.[9] The procedure has a sound physiological basis. Symptoms of heart failure appear when the work of the heart approaches the functional capacity of the organ. One of the prime determinants of the work of the heart is the volume of blood it pumps per minute The cardiac output, in turn, is primarily conditioned by the oxygen consumption, which, in its turn, is largely governed by the activity of the thyroid gland. Removal of the thyroid gland lowers the oxygen consumption of the body, and consequently the output and work of the heart. In fact, the cardiac output and work following thyroidectomy may be decreased proportionally even more than is the oxygen consumption (page 561). The basic conception of thyroidectomy for heart failure is to reduce the work of the heart to a level sufficiently below its functional capacity to eliminate the symptoms of cardiac insufficiency. The rationale in angina pectoris is similar. The requisite volume of coronary flow is largely a function of the work of the heart By thyroidectomy it is hoped to lower the indispensable volume of coronary flow to so much less than the narrowed coronary arteries can transmit that the relative ischemia which produces angina pectoris will disappear.

This theory that thyroidectomy alleviates heart failure or angina pectoris through the intermediacy of decrease in cardiac work is the one which—in addition to an observation by Levine[24] that subtotal resection of a normal thyroid gland in a patient with supposed masked hyperthyroidism relieved the heart failure present—led to the introduction of the operation. There is every reason to believe that the theory is fundamentally correct. However, other factors

may also enter. Two which have been studied are decreased sensitivity to epinephrin and interruption of nerve pathways.

It was observed by the originators of the procedure that some patients with angina pectoris obtain relief immediately after the operation and that the precordial discomfort of individuals with heart failure may also clear up at this time. Such immediate relief occurs before the fall in metabolic rate, which does not become significant before at least several days, and therefore cannot be due to decrease in cardiac work. Levine, Cutler and Eppinger[35] attributed this immediate relief to decreased sensitivity of the thyroidectomized organism to epinephrin; that epinephrin can produce anginal pain had previously been shown by Levine (page 417). However, Riseman, Gilligan and Blumgart,[33] using an intravenous drip of epinephrin, found no evidence of decreased sensitiveness in patients who had undergone thyroidectomy as long as the basal metabolic rate remained above −30 per cent, although it was present in some individuals with still lower metabolic rates. It would thus appear that the early relief of cardiac pain is not due to decreased sensitivity to epinephrin, although this factor may enter in individuals with very low metabolic rates.

In all probability, as demonstrated by Weinstein[34] and his associates, the early relief of pain is due to interruption of afferent nerve paths during the operation. They found that when a hemithyroidectomy was performed, pain was relieved only on the operated side. After a few weeks the pain returned on the operated side, to disappear on both sides when the metabolic rate was lowered by completing the thyroidectomy. The early relief of pain due to interruption of nerve pathways is thus transitory, a fact already known from experience with cervical sympathectomy in angina pectoris.

It has been objected to thyroidectomy that the operation will lead to the type of cardiac damage known as myxedema heart (page 590) and that, presumably through the intermediacy of hypercholesterinemia, the development and progress of arteriosclerosis will be favored. The actual validity of these objections remains to be established by experience. Since the operation is indicated only in those with a short expectation of life, if these deleterious consequences come on only after several years, they may well be taken in the bargain.

Indications and Contraindications.—Blumgart and his associates introduced total ablation of the thyroid gland because they found that partial thyroidectomy does not permanently depress the basal metabolic rate below normal. *Such relief of heart failure as is attained is purchased at the expense of myxedema.* It is true that the symptoms of myxedema can be largely controlled by the administration of thyroid extract, but nevertheless the induction of per-

manent hypothyroidism is so serious a matter as to circumscribe the indications for the operation to a small field. These indications are as follows:

1. Thyroidectomy is to be considered only in patients with heart failure or angina pectoris in whom life has become intolerable despite the application of other methods of treatment over so long a period as to demonstrate beyond cavil that they cannot help.

2. Despite the severe and otherwise hopeless nature of the disease, the physical condition of the patient must be good enough to indicate that there is little operative risk.

3. Patients in whom there seems to be strong likelihood that progressive myocardial lesions are present should not be operated upon. This applies particularly to active rheumatic carditis and recent coronary thrombosis, as well as to arteriosclerotic heart disease with changing electrocardiograms indicating progressive myomalacia even though there has been no major episode of coronary thrombosis. In such cases the likelihood that exacerbation of the myocardial lesions will neutralize any good effects of the operation is too great to justify the operation. Likewise, in syphilitic heart disease the chances of narrowing of the coronary mouths or other advances of the syphilitic process are too great to warrant the operation in at least the vast majority of cases.

4. Probably only those cases should be considered for operation in which bed rest, fluid and salt restriction, and the use of diuretics produce considerable improvement, although this is not sufficient or lasting for the patient to be up and about for any considerable time. For the occurrence of improvement as a result of measures which diminish the work of the heart lends encouragement to the belief that the greater diminution in the work of the heart due to thyroidectomy will aid the patient.

5. It does not seem wise to operate patients with a metabolic rate after protracted bed rest of less than −10 per cent. For if it is lower, one can scarcely hope to diminish the metabolic rate sufficiently, and yet avoid severe myxedema, to make a noteworthy difference in the work of the heart. Indeed, cases would seem preferable in which the metabolic rate is +10 or 20 per cent or more, as is so often true in heart failure even in the absence of thyrotoxicosis (page 141).

6. There should be no extracardiac factors—notably hypertension the malignancy of which is attested by papilledema or badly impaired renal function—which bid fair *per se* to terminate life before long. Thyroidectomy usually does not lower blood pressure; indeed, Schnitker, Van Raalte and Cutler[36] observed an average rise of 10 mm. in the systolic and diastolic pressures five months after operation.

It thus appears that *thyroidectomy is indicated in but a very small*

proportion of patients with heart failure or angina pectoris. Actually, the operation is a last resort when everything else has been tried without success and "there is nothing to lose." But the principle of "nothing to lose" must not inveigle one into an operation despite negligible hope of success merely because the patient is nearing the end

Evolution and Management of the Hypothyroidism.—Following the removal of the thyroid gland, hypothyroidism gradually develops. According to Gilligan *et al.*,[20] the fall in metabolic rate is usually evident by the end of the first week and reaches its lowest level by about the end of the first month. However, there is considerable individual variation in the rate at which the oxygen consumption falls, and the lowest levels may not be reached for six months (Schnitker *et al.*,[16] who consider the possibility of aberrant thyroid tissue in such instances). As a rule, the metabolic rate descends to −35 per cent or lower, and may reach about −45 per cent. Sooner or later, if thyroid extract is not administered, the classical symptoms and signs of myxedema make their appearance. Most often, this occurs between two and six weeks after operation. Gilligan and his associates found that by the end of the first month most of the patients exhibited dry skin, slight pallor, and sensitivity to cold, while after the second month such more serious symptoms as weakness, drowsiness, emotional irritability, and puffiness of the face or extremities made their appearance. There is great individual variation in the level of the oxygen consumption at which symptoms of myxedema appear; in some, they are manifest after a short time with a metabolic rate of −15 per cent, while in others they are pronounced only after weeks with a basal metabolism below −25 per cent. In addition to the oxygen consumption, the cholesterol content of the blood has been used as an index of the hypothyroidism; Epstein and Lande[17] long ago showed that in hypothyroidism the blood cholesterol rises and may reach levels surpassing 700 mg. per cent. However, the inverse proportionality between the cholesterol level in the blood and the clinical symptoms of hypothyroidism is not very close, though probably closer than that between these symptoms and the oxygen consumption.

Sooner or later the symptoms of myxedema become severe enough to necessitate the administration of thyroid extract. This should not be done merely because the basal metabolism is very low or the blood cholesterol high, but only when the subjective complaints of the patient are sufficiently severe to incommode him seriously. The object is to maintain as pronounced a state of hypothyroidism as possible without invoking intolerable symptoms of myxedema. There is no fixed level of basal metabolism or blood cholesterol to be aimed at, but perhaps most often a metabolic rate of about

—20 per cent is optimal. Usually, the administration of less than ½ grain of desiccated thyroid daily suffices, although if the hypothyroid symptoms are severe one may start with ½ grain. The greatest care is needed in the administration of thyroid extract, for an excess may promptly result in exacerbation of heart failure or angina pectoris.

Complications of the Operation.—Even in the best hands, there is an operative mortality. Blumgart[6] and his associates report that 6 of 75 patients succumbed within a week after operation All the deaths were due to postoperative pulmonary complications in patients with heart failure, none occurred in individuals with uncomplicated angina pectoris The main complications of the operation are recurrent laryngeal palsy and parathyroid insufficiency; the incidence of these, in serious form, is low in skilful hands. Surgical details are to be found in the papers of Berlin[7] and Cutler and Schnitker.[14]

Results of Thyroidectomy.—These have not been wholly concordant The largest experience has been in the clinics of Boston. Reports from three such clinics are as follows

The largest series is that from Beth Israel Hospital. Blumgart[8] and his colleagues report as follows· There were 50 patients with heart failure, mostly sufferers from rheumatic or arteriosclerotic heart disease, and 25 with angina pectoris. The ages ranged from eighteen to sixty-nine years Of the 50 patients with heart failure, 24 were able to work when last seen two to eighteen months after operation and 6 again regained compensation after recurrent heart failure There were 6 operative deaths and an equal number of subsequent deaths, while 2 were unimproved, and 6 had been recently operated upon Of the 25 patients with angina pectoris, 8 had complete relief when last seen, three to eighteen months after operation; 5 had infrequent attacks. 6 had recurrences after a period of complete relief; 4 had little or no relief; and 2 were recently postoperative. There were no operative deaths in the patients with angina, but 1 who had obtained complete relief for three months succumbed to coronary occlusion.

The results obtained by Levine and Cutler at Peter Bent Brigham Hospital are quoted by Means and Sprague[28] (see also Cutler and Schnitker[14]) as follows. Of 25 patients with heart failure operated upon from one to three years before: 6 showed great improvement, 5 moderate improvement, 2 slight improvement, and 12 no improvement (including 2 operative deaths). Of 29 patients with angina pectoris operated upon one to three years before. 11 showed great improvement, 10 moderate improvement, 4 slight improvement, and there were 2 operative deaths. In this series, Means and Sprague considered that results which were "worthwhile" were

obtained in 36 per cent of those with heart failure and 65.5 per cent of those with angina pectoris.

The results obtained by Means and Sprague[26] at Massachusetts General Hospital were not as favorable. They had 19 patients with heart failure and 2 with angina pectoris. Fifteen of their patients were dead at the time of writing. In only about one-fourth of their cases were the results obtained regarded as "worth-while." Means and Sprague believe that superior results might have been obtained with better selection and handling of the patients, and that then about 50 per cent of "worthwhile" results might be secured. While they have not abandoned the operation, they had not recommended it for six months prior to writing. Results of about the same order as those of Means and Sprague were obtained by Ochsner and Gillespie[29] and Maes.[25] More recently, Bourne and Ross[11] obtained what they considered worth-while results by thyroidectomy in 12 patients with angina pectoris.

The writer's personal experience with thyroidectomy has been small, and confined almost entirely to patients with heart failure. Several were not appreciably helped. However, one man who was hopelessly bed-ridden as a result of hypertensive and arterio-sclerotic heart disease was able to get about, though not capable of work, more than two years after operation. The life of a woman in a similar condition was, I feel confident, prolonged at least a year by thyroidectomy.

Further experience is needed to delimit the field of thyroidectomy more closely. From present indications, which may have to be revised, the field of usefulness of the operation would appear to be a very circumscribed one. Thyroidectomy for heart failure or angina pectoris has not been performed on the ward service at Mount Sinai Hospital in the past three years. Nevertheless, in a small number of carefully selected patients whose outlook is other-wise hopeless, thyroidectomy may offer the possibility of a period of at least tolerable survival. It would appear that good results are more likely in patients with angina pectoris than in those with heart failure. Even though the number of patients who can be helped by the operation proves small, the profession is indebted to the originators of the operation for a new approach to the treatment of heart failure and angina pectoris, and one which may lead much farther.

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CHAPTER XXXVI

THE TREATMENT OF HEART FAILURE: IV. THE MANAGEMENT OF DISTURBANCES IN RHYTHM

AURICULAR FIBRILLATION

The treatment of patients with auricular fibrillation differs notably in the continuous and paroxysmal forms, and in accord with whether or not heart failure is present.

Most often, complete arrhythmia is continuous and accompanied by more or less heart failure. In addition to rest, appropriate diet, etc, the treatment of such cases consists in the use of digitalis. Digitalization is a remedy for the heart failure resulting from auricular fibrillation and not for the auricular fibrillation as such —it does not eliminate the arrhythmia and may in fact tend to perpetuate an otherwise paroxysmal fibrillation. But the elimination of the heart failure, despite the persistence of the fibrillation of the auricles, yields some of the most spectacular therapeutic results enjoyed by the physician. Digitalis should be given in doses sufficient to maintain the ventricular rate as close to normal as feasible In fact, some patients feel best with the ventricular rate about 60 per minute In the large majority of instances, apart from the cases due to hyperthyroidism in which operation restores the rhythm to normal, digitalis has to be administered more or less continuously for the rest of the patient's life. Exceptionally, digitalis maintains individuals with auricular fibrillation in excellent compensation for ten or more years. Details regarding the administration of digitalis are given in Chapter XXXIV.

Quinidine.—In patients in whom auricular fibrillation is accompanied by little heart failure, or in whom the latter has been largely eliminated by digitalization, the use of quinidine comes into question While digitalis is purely a remedy for the heart failure resulting from auricular fibrillation, quinidine is a drug which tends to restore sinus rhythm, *i e.*, it is a treatment for the arrhythmia *per se* The manner in which quinidine restores sinus rhythm is not clear and will not be discussed in detail here (Lewis[13]). On the basis of the prevalent theory that auricular fibrillation is due to a self-perpetuating ring of excitation (circus movement) in the auricular musculature, the drug presumably acts by abolishing the circus movement so that the sinus node again resumes command. Experimental findings show that quinidine retards conduction along the muscle fibers and prolongs their refractory period. Both these factors may be concerned in slowing and ultimately abolishing circus

movement, but in the case of auricular fibrillation the prolongation of the refractory period is believed to be the more important.

Quinidine is not always an innocuous remedy, for which reason careful discrimination is necessary in its use. In only a small fraction of patients with auricular fibrillation is quinidine indicated. The main field is in those exceptional instances in which the chief complaints of the patient are due to the fibrillation itself, and there is reason to believe that if regular rhythm is restored and maintained the comfort of the patient will be greater. The results obtained with quinidine rarely justify its use in cases in which there are severe organic lesions of the heart, notably tight mitral stenosis or coronary arteriosclerosis with widespread myocardial damage. Under these circumstances, the drug probably has more than its usual quota of danger and, even if normal rhythm is attained, fibrillation usually soon recurs. In patients with auricular fibrillation due to rheumatic or arteriosclerotic heart disease who are well controlled by digitalis, it is rarely wise to attempt to restore sinus rhythm with quinidine. Since a greatly enlarged left auricle in mitral stenosis usually contains multiple clots, the drug should not be given when such enlargement is found fluoroscopically because of the danger of embolization after restoration of regular rhythm. The same is true with a previous history of emboli Old age and long duration of auricular fibrillation have been considered as contraindications, but sometimes good results are obtained under these circumstances. The best results are obtained in auricular fibrillation without other evidences of heart disease, in paroxysmal fibrillation, and when the arrhythmia persists after thyroidectomy.

The proportion of cases restored to normal rhythm varies with the type of case. In 1058 cases compiled by Eismayer,[8] regular rhythm was restored in 58 5 per cent, the same occurred in 55.9 per cent of 606 cases collected by Burwell and Dieuaide.[4] The more recent the inception of the arrhythmia and the less the cardiac enlargement and other evidences of organic heart disease, the more likely the restoration of normal rhythm and especially its maintenance. Wolff and White[24] obtained restoration of regular rhythm in all of 7 patients with auricular fibrillation but no other indications of heart disease. (See their paper for statistical details) Active rheumatic infection and severe heart failure militate against success with quinidine. In a high proportion of cases in which normal rhythm is restored by quinidine, fibrillation recurs between hours and years later, in a decided majority of the cases that I have observed, the duration of regular rhythm did not exceed a few months. Often, however, when a patient suffers considerably from palpitation or other symptoms due directly to the arrhythmia, the result is well worth while even though regular rhythm lasts only a few months. But longer restoration of sinus rhythm is not rare,

Wolff and White report that of 38 patients in whom auricular fibrillation was abolished by quinidine, 11.7 per cent still had regular rhythm from six to seven years later. If the arrhythmia recurs it may or may not be terminated again by quinidine.

While restoration of regular rhythm with quinidine often increases the comfort and working capacity of the patient, the weight of evidence indicates that it does not notably increase the average duration of life. Wolff and White found approximately the same death rate in those of their patients in whom quinidine restored regular rhythm and in those in whom it failed.

Administration.—The administration of quinidine for auricular fibrillation is usually initiated in bed, but Weisman[20] has reported excellent results in ambulatory patients; I have also given quinidine to ambulatory patients with auricular fibrillation on repeated occasions without accident. Because some individuals have an idiosyncrasy to the drug, the course of treatment should be preceded *by a probatory dose of 0.1 gram of quinidine sulphate.* The next day two doses of 0 2 gram may be given and the number of doses increased one daily until regular rhythm is attained or a maximum of about 2 or 2 5 grams daily is given. It appears that the maximum effect of a dose of quinidine is within two or three hours, for this reason, if administration during the day is not successful, it should also be given at four-hour intervals through the night. More than 10 grams of quinidine sulphate has been given within a day, but the risks of such huge doses would seem far to outweigh the possible advantages. When the rhythm returns to normal, the patient should be given a "maintenance dose" of about 0.3 gram daily; after a time, the drug may be discontinued to see if regular rhythm is maintained without it If the above-mentioned doses fail to restore sinus rhythm within about ten days, quinidine should be stopped for some weeks; then, another attempt may be made and is sometimes successful. The transition to normal rhythm is probably usually through a period of auricular flutter, which may be detected clinically. It is sometimes desirable to continue quinidine for a long time; Fahr[8] has given 12 grains a day for as long as ten years.

Because some of the effects of digitalis on the heart muscle and the vagus nerve are the opposite of those of quinidine, it has been thought that digitalization retards restoration of normal rhythm by quinidine (Barrier[2]) and that quinidine should not be given until some time after digitalis has been stopped. This conception does not seem to be borne out in practice. Wolff and White found that quinidine is more apt to restore regular rhythm after the patient has been digitalized sufficiently to invert the *T* wave in Leads I and II, and that the amount of quinidine required tends to be less under these circumstances. Since, theoretically, digitalis should favor the continuance of fibrillation through its effects on the

refractory period and conduction in the muscle fibers, these findings are perhaps to be attributed to improvement of even slight degrees of heart failure by digitalis favoring the action of quinidine. If the patient with auricular fibrillation has heart failure, the attempt should be made to eliminate the latter with digitalis before quinidine is started. Under such circumstances, the writer has repeatedly continued the digitalis after quinidine was started without observing ill effects from the simultaneous administration of the two drugs

During the administration of quinidine, careful watch should be kept for side effects. The drug is to be discontinued on the appearance of nausea, vomiting, diarrhea, headache, vertigo, tinnitus, deafness, urticaria or other skin eruptions, a feeling of heat throughout the body or disorientation. Because of the depressing effect of quinidine on vagal tone and the reduction in the rate of the auricular circus movement so that more impulses are transmitted by the bundle of His, quinidine often accelerates the ventricular rate But if the latter exceeds 120 per minute, the drug should be stopped, for there is the possibility of ventricular tachycardia

When quinidine is administered to properly selected patients and following the above-mentioned precautions, fatal accidents are great rarities. The best known of these—but, it is to be repeated, a great rarity—is embolism due to loosening of the clot from the left auricle when the latter starts coordinated contraction The danger of embolism has been exaggerated, Viko, Marvin and White[19] observed *embolism in 4 5 per cent of their patients who did not receive quinidine* and in 3.1 per cent of those who were given the drug Sudden death not due to embolism has also been observed, while the mechanism remains to be elicited, it may be due to ventricular fibrillation or, according to White,[22] perhaps to cardiac standstill as a result of depression of both the sino-auricular and auriculo-ventricular nodes so that when the circus movement is brought to a halt the heart has no pacemaker.

Paroxysmal Auricular Fibrillation.—Apart from the extremely rare instances in which heart failure develops during a paroxysm, digitalis is best omitted because of its tendency to perpetuate the arrhythmia. Quinidine often terminates a paroxysm and may be an efficient prophylactic.

Thyrotoxic auricular fibrillation is discussed on page 789.

AURICULAR FLUTTER

During brief paroxysms of auricular flutter ending spontaneously, no therapy is indicated other than rest and perhaps a sedative if the patient is alarmed Pressure on the eyeball or carotid sinus may temporarily slow the ventricle and cause dropped beats by increasing the degree of block. But this measure does not abolish

the flutter, and I had a disagreeable experience when pressure on the eyeball caused ventricular standstill for about ten or fifteen seconds with loss of consciousness and twitchings. Some individuals who have had many attacks continue at their occupation during a paroxysm. Maintenance doses of quinidine or digitalis may diminish the number of paroxysms or even abolish them. In some individuals, paroxysms of auricular flutter are excited by exertion or excitement; such persons should, of course, guard against the exciting cause.

If an attack of auricular flutter does not pass away within a few hours, it should be treated with either digitalis or quinidine. Digitalis is more often efficacious and should be tried first. Treatment may be initiated with about 0.6 gram of the powdered leaf daily in divided doses, and this amount subsequently diminished in accord with the response. The first effect is usually slowing of the ventricular rate as a result of augmentation of the auriculo-ventricular block which is almost always already present before treatment. The block may be increased from 2 to 1, 3 to 1, 4 to 1, or even more, with corresponding slowing of the pulse and improvement in the symptoms and, if these are present, the signs of heart failure. Not rarely, the pulse becomes irregular as a result of the production of a fluctuating auriculo-ventricular block. Exceptionally, sinus rhythm returns during the administration of digitalis. But the most characteristic course of events is for the continued administration of digitalis to result—presumably as a consequence of decrease in the refractory period of the auricular musculature and increase in the rate of the circus movement—in transformation of the flutter into auricular fibrillation. Digitalis should then be withheld, for this may be followed by restoration of normal rhythm. Even if digitalis fails to restore normal rhythm, it helps the patient by slowing the ventricular rate.

If digitalis does not restore normal rhythm, the administration of quinidine is to be tried in the same fashion as in the treatment of auricular fibrillation. Presumably through retarding conduction within the auricular muscle and increasing the refractory period, quinidine slows the circus movement and auricular rate, and may thus abolish the former with consequent return of normal rhythm. As a result of the depression of vagal tone by quinidine, the ventricle may be accelerated and even respond, in consequence of the better auriculo-ventricular conduction due to vagal depression, to each auricular contraction when the rate of the auricle is slowed. Acceleration of ventricular rate is thus a stage in the quinidine treatment of auricular flutter.

The results obtained in the treatment of auricular flutter are exemplified by the 22 cases of Cowan and Ritchie[8]: In 4 the paroxysm ended spontaneously; in 2 flutter was transformed into

fibrillation by strophanthin or strophanthus, normal rhythm being subsequently restored; in 1 normal rhythm was restored while digitalis was being taken; in 8 flutter was converted into fibrillation by means of digitalis and in 4 of these normal rhythm was restored after digitalis was discontinued, in 3 normal rhythm was restored by means of quinidine; 4 cases were quinidine-proof. In Parkinson and Bedford's[15] 52 cases, digitalis restored normal rhythm, established auricular fibrillation, and failed to abolish flutter with about equal frequency. There are rare cases of auricular flutter which persist for long periods despite all therapeutic measures.

In rare instance, oricular flutter is associated with a ventricular rate so rapid—equal to the auricular—that extreme heart failure, sometimes with syncope and other manifestations of cerebral ischemia, results. The outcome may be fatal. Here, urgent measures are required. The attempt should be made to slow the ventricular rate by pressure on the eyeball or the carotid sinus. Strophanthin or digitalis may be given intravenously (providing they have not been given in the near past), sometimes with gratifying results. The intravenous injection of quinidine sulphate (0.2 gram, well diluted) may be tried if digitalis fails, but is risky. There was an excellent result in the only instance of auricular flutter in which I saw this treatment tried.

PAROXYSMAL TACHYCARDIA

Many, if not most, patients with auricular or nodal paroxysmal tachycardia have attacks at such infrequent intervals and of so slight severity that treatment is hardly worthwhile They are to be reassured and told to rest until the paroxysm passes. But if, as is sometimes the case, they feel better and the attack passes more rapidly if they walk around or continue at their activities, they may be permitted to do so. It is true that this is not always without danger; a man who kept about during his attacks finally sustained a severe injury to his skull when he fell as a result of the onset of an attack while on the subway stairs. Often, the patient learns some simple procedure that terminates an attack. These maneuvers usually function through vagal stimulation and include holding the breath, drinking ice-water, swallowing hard, inducing vomiting, turning the neck, or hanging the head low from the side of the bed.

Sometimes, vagal stimulation through pressure on the carotid sinus or the eyeball abruptly terminates an attack. Pressure on the right carotid sinus should be tried first, and if this fails the more painful ocular pressure may be attempted. Carotid sinus or ocular pressure is effective only in auricular or nodal tachycardia but not, because of the lesser susceptibility of the ventricular muscle to

vagal influence, in the ventricular form; and even in the former types it succeeds in only a small minority of the cases.

The powerful stimulation of the vagus by acetyl-beta-methylcholin has recently been invoked to terminate attacks of supraventricular (auricular or nodal) paroxysmal tachycardia. By injecting this drug subcutaneously, Starr[18] promptly terminated 66 of 75 attacks in 37 patients He found that older patients require a larger dose. He gave 20 or 30 mg. to younger patients and 50 mg. to those past fifty years. His procedure is first to try carotid sinus pressure If this fails, acetyl-beta-methylcholin is injected subcutaneously. Unless the attack stops promptly, the site of injection is massaged, which sometimes brings success. If not carotid sinus pressure is tried, and if this also fails, a larger dose is injected one-half hour later. Among the undesirable side effects of acetyl-beta-methylcholin which frequently occur are nausea, vomiting, syncope, and, in individuals with asthma, asthmatic attacks. If severe, these side effects may be abolished by the injection of atropine.

If the attack persists beyond a few hours despite the above measures, quinidine should be tried, it cuts short some, though by no means all, attacks. Five doses of 0.3 gram of quinidine sulphate at intervals of two hours may be given daily. If this fails, larger doses may be tried throughout the day and night. In urgent situations, quinidine sulphate (0.2 gram, well diluted) has been given intravenously and may stop the attack spectacularly, but I witnessed a fatality following such an injection. In the ventricular tachycardia of coronary thrombosis, a very serious condition, Levine[11] obtained excellent results from the oral administration of quinidine (page 781). Quinidine is also the drug of choice in ventricular paroxysmal tachycardia occurring under other circumstances.

If quinidine fails in auricular or nodal tachycardia, digitalis should be tried. In view of the possibility that digitalis may perpetuate the rhythm or even induce ventricular fibrillation, it would appear that the drug is contraindicated in ventricular tachycardia. But surprisingly enough, in view of the tendency of digitalis to induce ectopic rhythms, the drug may stop attacks of auricular or nodal tachycardia. Digitalis would appear to be especially indicated in the cases in which cardiac dilatation supervenes By the intravenous injection of digitalis in auricular tachycardia, Wilson and Wishart[23] produced first slowing of the heart and then cessation of the paroxysm Barrier[1] terminated 6 of 8 cases of auricular or nodal tachycardia by the intravenous injection of 5 cc. of digalen, repeated in forty-five minutes. Or 0.5 mg. of strophanthin may be injected The manner in which digitalis terminates auricular tachycardia is not clear; that it is at least sometimes through the intermediacy of vagal stimulation is indicated by Barrier's observation that in one of his cases of auricular tachycardia digitalis did not

restore sinus rhythm after atropine, although it did so on other occasions.

If there are frequent attacks of paroxysmal tachycardia, maintenance doses of quinidine sometimes lessen the frequency or even abolish them completely. Digitalis has also been used to diminish the frequency of attacks of supraventricular tachycardia, but I have no experience with the method

Recently, Harkavy (to be published) has observed 4 cases of paroxysmal tachycardia which he attributes to allergy to foods, and in which the attacks ceased when the offending foods were eliminated from the diet Further observations along these lines are much to be desired.

EXTRASYSTOLES

In the vast majority of instances, premature contractions not associated with evidence of organic heart disease need no treatment. If the patient is aware of their existence, or has been told of them by a physician, every effort should be made to convince him that they are innocuous. Sometimes, the effectiveness of such reassurance is enhanced by the administration of bromides or other sedatives, but usually the wiser course is to assure the patient that he needs no medicine If he has acquired the unfortunate habit of feeling his pulse to detect irregularities, this should be stopped. Sometimes, extrasystoles are due to tobacco and disappear when smoking is eschewed. But if cessation of smoking has no effect on the irregularity, or if the latter is not very annoying, there is no reason for depriving the patient of the pleasure. Coffee also appears to be a rare cause of extrasystoles In individuals with gall-bladder disease, premature contractions sometimes disappear after operation. When the premature contractions are sufficiently frequent to cause annoyance, quinidine sulphate, in doses of 0 2 gram, three times daily, may diminish the number or even abolish them. According to Wenckebach,[21] the effectiveness of this treatment (he used quinine) is enhanced by the addition of about 1 mg. of strychnine sulphate to each dose Paradoxically, while digitalis often produces premature contractions, it has repeatedly been observed that the administration of the drug sometimes abolishes spontaneous extrasystoles; this has been confirmed for both auricular and ventricular premature beats by the careful observations of Otto and Gold.[14] But there are many cases in which neither quinidine nor digitalis helps Atropine has been used for the treatment of premature contractions, but Otto and Gold found that the number is lessened only when the rate of the heart is markedly accelerated. They also found that exercise and epinephrin increase the frequency of ectopic beats

When extrasystoles appear in individuals with organic heart disease they likewise call for no special treatment. However, they occasionally presage the development of paroxysmal tachycardia or auricular fibrillation and hence call for close observation of the patient. The same is true when ventricular extrasystoles appear after coronary thrombosis, when they may herald more serious arrhythmias. Under these circumstances, it is generally wise to try to abolish them with quinidine, which may serve as a prophylactic of the more dangerous disturbances of rhythm.

ALTERNATION OF THE HEART

The pulsus alternans is a manifestation of heart failure and treatment is directed toward the latter. Sometimes, successful digitalization is followed by disappearance of the alternation.

HEART BLOCK

The lesser degrees of auriculo-ventricular block, revealed by prolongation of the auriculo-ventricular conduction time or even dropped ventricular beats, require no therapy directed specifically to the conduction disturbance. However, if the impaired conduction accompanies heart failure requiring digitalis, the latter should be administered cautiously with frequent observation to detect increase in the degrees of block In a careful study, Blumgart and Altschule[3] found that the administration of therapeutic doses of digitalis to patients with partial heart block and heart failure had little effect on auriculo-ventricular conduction.

In complete auriculo-ventricular dissociation, likewise, treatment for the conduction disturbance is not called for unless there are Stokes-Adams attacks. In the large majority of instances, such attacks are due to more profound slowing of the ventricles or even ventricular standstill (page 279). In such cases, the frequency of the attacks can often be diminished, or their complete disappearance for a time brought about, by the administration of drugs which enhance, the excitability of the idioventricular pacemaker which initiates ventricular systole in the absence of impulses along the bundle of His. The most effective drug of this type is epinephrin. Cullis and Tribe[7] showed that following section of the auriculo-ventricular bundle in cats and rabbits epinephrin accelerates both the auricles and ventricles. The same was subsequently demonstrated in human heart block, and Phear and Parkinson[14] showed that epinephrin may abolish Stokes-Adams attacks by accelerating the ventricles. The subcutaneous or intramuscular injection of 0.5 to 1 mg of epinephrin controls most Stokes-Adams attacks within a few minutes. Feil[10] warns against the intravenous injection of epinephrin during the attacks because of the danger of grave

reactions. Sometimes, repeated injections must be given at intervals of a few hours as the effect of the drug wears off and cerebral phenomena reappear. There need be no hesitation about injecting epinephrin subcutaneously in cases of heart block and the Stokes-Adams syndrome due to coronary thrombosis; under these circumstances, the drug may be life-saving. When the Stokes-Adams attack is due to complete standstill of the ventricles, the absence of circulation would appear to render peripheral injection of the drug useless and necessitate intracardiac injection; Levine and Motton[12] had success with such an injection. While epinephrin is of great value and even life-saving in the more common form of Stokes-Adams syndrome due to ventricular slowing, Schwartz and Jezer[17] point out that it may be harmful and is strongly contraindicated in the exceptional instances of the syndrome due to paroxysmal ventricular fibrillation (page 280). In two patients whose Stokes-Adams attacks were due to paroxysmal ventricular fibrillation, Schwartz and Jezer brought on paroxysms by the injection of epinephrin, and they also found that injection of epinephrin during ventricular fibrillation seemed to prolong the mechanism.

Ephedrin has much the same, though a less powerful but longer lasting, effect as epinephrin on the ventricular rate in complete heart block and on Stokes-Adams attacks In a patient with frequent attacks, Wood[25] prevented the Stokes-Adams syndrome for eighteen months by the oral administration of 24 mg of ephedrin sulphate once or twice daily; on discontinuance of the drug, the attacks reappeared.

Cohn and Levine[5] found that barium chloride increases the irritability of the idioventricular pacemaker and controls some Stokes-Adams attacks The dose of barium chloride is 30 to 60 mg., three or four times daily, by mouth. However, barium chloride—as well as thyroid extract and atropine, which have also been used—are not nearly as effective as are the sympathicomimetic drugs just mentioned.

A few instances are on record in which heart block in luetic heart disease, presumably due to gummatous lesions in the vicinity of the bundle of His, was cleared up by antiluetic treatment.

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CHAPTER XXXVII

THE TREATMENT OF THE INDIVIDUAL DISEASES WITH HEART FAILURE OR ANGINA PECTORIS

RHEUMATIC HEART DISEASE

In the treatment of rheumatic heart disease, the physician strives toward two goals, the paths to which do not always coincide: inactivation of the rheumatic infection and elimination of cardiac strain and failure. The relative importance of these objectives varies, not only in different patients but also in the course of the same case. From the point of view of the immediate therapeutic objective, three groups of cases may be differentiated:

1. Patients with rheumatic infection in whom there is no evidence of heart failure. Cases of this type are common despite the fact that the myocardium is implicated in practically every instance of rheumatic infection, and occur even where the cardiac implication is revealed by the physical or electrocardiographic findings. Such a state of affairs is present in most initial attacks of rheumatic fever. although exceptionally evidences of heart failure develop even during the first bout of rheumatic activity. Some patients go through repeated exacerbations of rheumatic fever without evidence of heart failure, but this is decidedly unusual. In these cases, because of the absence of heart failure, the therapy is entirely that of the rheumatic infection *per se*.

2. Patients with both florid rheumatic activity and heart failure. The vast majority of instances of heart failure in children are of this nature, the cardiac insufficiency being caused by the exacerbation of rheumatic activity in the heart. The same is true of a high proportion of cases of failure of the rheumatic heart in young adults and of some of those in the elderly. Here, the treatment consists of measures directed toward both the rheumatic infection and the heart failure.

3. Patients with long-standing rheumatic heart disease in whom cardiac failure develops in the absence of florid rheumatic infection. This is rare in the young but common in those past thirty years. It is true that a high proportion of such individuals have low-grade rheumatic act vity at the time, as manifested at necropsy by scattered Aschoff bodies and perhaps recent verrucæ on the cusps. But the activity, when present, is of such low grade that it is not revealed by fever, leukocytosis, or acceleration in sedimentation rate, and is not manifested by arthritis. Since none of the manifestations known to be influenced by salicylates or other antirheumatic

drugs are present, the physician must perforce confine his therapeutic activities to the management of the heart failure.

General Measures in the Treatment of Active Rheumatic Infection.—Patients with active rheumatic infection belong in bed. Because of the frequently profuse perspiration, they should have absorbent bed-clothes and be protected from draughts. If there is arthritis the painful joints should be swathed in flannel and efforts be made to avoid jolting the bed. With pericarditis it is customary to apply an ice-bag to the precordium, but it is doubtful that this is of more than psychotherapeutic value. When chorea is present, quiet is of especial importance.

In view of the elevated metabolism due to the fever, the diet should be ample and include an adequate protein ration. That any special dietary régime has specific value in rheumatism has not been shown. Rinehart[49] and his associates found that infection superimposed upon chronic scurvy in guinea-pigs results in lesions which they considered histologically similar to those of rheumatic infection They also adduced epidemiological and other evidence that deficiency of vitamin C (ascorbic acid) is concerned in the pathogenesis of rheumatic fever. However, Perry[47] and Sendroy and Schultz[52] have shown that vitamin C deficiency is not always present in rheumatic infection, and there is no evidence that the administration of large amounts of vitamin C, as has been suggested, exerts a specifically favorable effect on the rheumatic infection.

Drugs in the Treatment of Rheumatic Infection.—The salicylates are by far the most generally valuable drugs in the treatment of active rheumatic infection. This is true despite the fact that several generations of clinical observation indicate that the administration of salicylates does not abbreviate the duration of an exacerbation of rheumatic activity and while the disease is active the symptoms recur when salicylates are withdrawn. Miller[41] found that the period of hospitalization is not abbreviated by the administration of salicylates. But although the salicylates do not shorten a rheumatic attack, they have two very favorable effects, namely, to diminish the temperature if fever is present, and to decrease the pain and swelling of joints implicated in rheumatic arthritis. How these beneficent effects are produced is entirely unknown; the fact that the duration of the attack is not shortened would indicate that the salicylates have neither a bactericidal action on the unidentified causative organism of rheumatic fever nor a stimulating effect on the development of immunity. The most important question from our present point of view, that of the effect of the salicylates on the imflammatory process in the heart, is as yet obscure. Since the salicylates induce the subsidence of the exudative inflammation in the joints, it might be assumed that they have a similar action on exudative phenomena in the heart. However, so far as I am aware,

it has not been demonstrated that salicylates accelerate the resorption of rheumatic pericardial effusions, although this should be studied more carefully with the roentgen-ray. And in the myocardium and endocardium, from a very early stage, rheumatic inflammation is predominantly proliferative rather than exudative in nature; we do not known what are the effects of salicylates on the proliferative process. Nor has clinical observation furnished an unequivocal answer to the question whether the salicylates affect rheumatic carditis. Coombs,[10] who studied rheumatic disease intensively for several decades, stated that "my experience leads me to believe that the administration of salicylates does limit the extent of the cardiac lesions." On the other hand, it is an everyday experience to observe the progression of rheumatic carditis while the patient is receiving large doses of salicylates It would thus appear that the utility of salicylates for other than combating fever or arthritis is still not proved, and the advisability of administering these drugs for either the treatment or the prophylaxis of rheumatic heart disease in the absence of fever or arthritis is still *sub judice*. Presumably, the elimination of fever by salicylates helps the heart by diminishing its work. Attempts have been made to prevent the reactivation of rheumatic infection by the administration of salicylates to children with quiescent rheumatic diease (Leech[30]), but the utility of this procedure has not been proved. It has the disadvantage that it might mask the onset of rheumatic activity.

Of the salicylates, the most generally useful is sodium salicylate. In florid rheumatic infection with fever and perhaps arthritis, it should be administered in large initial doses. Because of the individual variability of the amount producing toxic manifestations, sodium salicylate is best given in divided doses. The addition of an equal amount or more of sodium bicarbonate appears to lessen the tendency to gastric irritation. The drugs may be given in enteric-coated capsules or in such a vehicle as peppermint water. In an adult 15 to 20 grains of sodium salicylate may be given hourly for eight doses or discontinued before if toxic manifestations develop. The same or a smaller amount may be given the next day and progressively smaller dosage administered as indicated by the arthritis and temperature. If gastric irritation prevents the oral administration of sodium salicylate, it may be given by rectum; after a cleansing enema 100 to 150 grains of sodium salicylate are given in 5 or 6 ounces of starch water to which 15 minims of tincture of opium have been added. The same or, if needed, a larger dose may be repeated daily. However, it should be remembered that vomiting due to salicylates may not be the result of gastric irritation but rather produced by central action; it is then accompanied by other toxic effects and may also follow rectal administration. Salicylates may also be given intravenously (2 grams of sodium

salicylate in 10 per cent aqueous solution); while the action is rapid, this method would seem rarely called for. Some physicians prefer acetylsalicylic acid to sodium salicylate on the ground that it is less apt to cause gastric irritation. However, hypersensitivity to acetylsalicylic acid is probably more common than to sodium salicylate. The dosage is about two-thirds that of sodium salicylate While methyl and strontium salicylates have been used, they present no advantages and severe intoxication may occur from large doses of the former. With all the salicylates, close watch is to be kept for evidences of salicylism—fulness in the head, headache, tinnitus, vertigo, deafness, vomiting, and rarely mental or visual disturbances. While albuminuria may result, renal damage of consequence does not seem to occur. Many physicians endeavor to attain maximum saturation with salicylates by increasing the dose until tinnitus is produced. However, since it is not yet demonstrated that the salicylates exert a favorable effect on the cardiac lesions, such a procedure would seem to invite unnecessary discomfort if the therapeutic effects on the fever and arthritis are attained with smaller doses.

The drugs that have been most widely used as substitutes for the salicylates are cincophen, neocincophen, and amidopyrin. The cincophens are given in the same dosage as the salicylates, and often have the same effect on the fever and arthritis. But since in rare cases, presumably in individuals with some as yet obscure predisposition, the cincophens produce hepatic degeneration, it would seem wise to reserve these drugs for use in the very exceptional cases in which the salicylates are ineffective. The use of amidopyrin in rheumatic infection has been studied with special care by Schultz.[82] He found that in doses of between 10 and 30 grains daily amidopyrin generally controls the fever and arthritis. Schultz found that in these doses amidopyrin does not cause gastric irritation, which has the advantage when digitalis is also being given that it permits the easier recognition of excessive doses of digitalis. However, since amidopyrin has a toxic and depressing effect on the bone marrow in rare individuals, the writer prefers not to use the drug unless the salicylates fail or produce toxic symptoms. There is no evidence that either cincophen or amidopyrin shortens rheumatic exacerbations or influences the carditis.

As in all infections, numerous clinicans have used sulfanilamide and other sulfonamide derivatives in the treatment of rheumatic fever (*cf.* Swift, Moen and Hirst[83]). So far, these drugs appear to be without therapeutic value in active rheumatic infection, and toxic manifestations seem to be especially frequent in these hyperreactive individuals. On the other hand, it is quite likely that protracted administration of sulfanilamide to individuals who have suffered from rheumatic infection serves to lessen the incidence of

recurrences. This is not surprising, because it seems well established that, whatever the fundamental etiology of rheumatic fever, exacerbations are often evoked by infections with hemolytic streptococci (cf. Coburn[7]). Thomas and France[63] administered during two winters 15 to 20 grains daily of sulfanilamide to 30 individuals with recent acute rheumatic fever, and found that none developed any manifestation of active rheumatic infection. If such continuous and protracted administration of small doses of sulfanilamide proves to be without deleterious side effects, the prophylactic use of the drug in rheumatic individuals may prove of the highest importance.

Iron is often a valuable remedy for the hypochromic anemia that develops during active rheumatic infection. The anemia may require transfusion.

Various vaccines and serums have been introduced for the treatment of rheumatism, but their value has not been demonstrated. The same is true of non-specific protein therapy Nor does roentgen irradiation of the heart, used by Levy and Golden,[34] seem of established value.

Treatment of Heart Failure During Florid Rheumatic Infection.—When heart failure is produced by exacerbation of rheumatic carditis, much the usual treatment for cardiac insufficiency, as already described, is in place However, except in cases with auricular fibrillation, digitalis often has little effect on the heart rate or the symptoms of heart failure as long as the infection is active and fever is present. In auricular fibrillation, despite the presence of fever, the response to digitalis may be excellent When edema is present, the mercurial diuretics are often valuable, producing profuse diuresis when digitalis has failed to do so. Because of the presence of fever and sweating, fluid and salt intake should not be restricted as in other forms of heart failure. Salicylates and other antirheumatic drugs (page 764) should be used as in the absence of heart failure; whether or not they affect favorably the inflammatory process in the heart, the reduction of fever and the effect on the joints when arthritis is present are desirable. In edematous patients the writer has used acetylsalicylic acid or other antirheumatic drugs in place of sodium salicylate because of the apprehension that the administration of the sodium ion might aggravate the water retention; whether this fear is justified in fact remains to be demonstrated. It will often be found that all measures to overcome the heart failure are unsuccessful until the rheumatic activity subsides, after which the cardiac insufficiency improves spontaneously.

Removal of Foci of Infection.—A high proportion of cases of rheumatism are initiated by sore throat, and the same sequence of events is common during acute exacerbations of rheumatic activity. In these sore throats, tonsillitis and inflammation of the other

lymphoid collections constituting Waldeyer's ring are generally the predominant or a prominent feature. By those who regard rheumatic disease as a manifestation of focal infection, the lymphoid tissue of the throat has been assigned a predominant place as a focus, and in the allergic modification of this theory, the throat is generally considered the most frequent source of sensitizing infection. Because of these facts and theories, much was expected of tonsillectomy and adenoidectomy in the treatment of rheumatic activity and especially in the prophylaxis of subsequent attacks. These hopes have been fulfilled in but slight degree. It is generally agreed that tonsillectomy rarely, if ever, cuts short an attack of florid rheumatic infection, and indeed the severity of the case is sometimes aggravated following the intervention. For this reason, operation is now hardly ever carried out during the height of a rheumatic exacerbation. The value of tonsillectomy as a preventative of initial rheumatic infection or of subsequent exacerbations in a rheumatic individual has given rise to more difference of opinion. Comparing the incidence of rheumatic infection in 20,000 children who had had tonsillectomy with that in 28,000 who had not, Kaiser[27] concluded that rheumatic infection is less common after tonsillectomy, but the difference in incidence in the two groups was not great. Wilson, Lingg and Croxford[69] found that tonsillectomy has no considerable effect on the incidence of recurrences in rheumatic children; the latter became less common with advancing years whether or not the tonsils had been removed. Of 194 rheumatic children observed for one to eight years by Smith and Sutton,[53] tonsillectomy was followed by improvement in 28 per cent, by no improvement in 68 per cent, and by aggravation of the condition in the remainder. These findings speak definitely against the advisability of routine tonsillectomy in individuals with rheumatic heart disease, a practice all too prevalent in the past. The indication for tonsillectomy in rheumatic individuals would seem to be the presence of definite infection in the tonsils, especially if there is a history of sore throat. And even when the tonsils are definitely infected, it is wiser to postpone the tonsillectomy until an acute exacerbation of the rheumatic infection has subsided; otherwise, severe reactions will occasionally be encountered. Coburn[7] has observed frequent mild exacerbations and a number of severe recrudescences following tonsillectomy in rheumatic individuals; I have made similar observations. Coburn not infrequently encountered prolongation of the P–R interval in the electrocardiogram after tonsillectomy in rheumatic patients which was not present twenty-four hours before the operation. Even though the removal of the infected tonsils does not prevent future exacerbations, it often, just as in non-rheumatic children, results in gain in weight and improvement in the general physical condition.

I have not known the removal of infected teeth or treatment of sinus infections to have any effect on the course of rheumatic infection. The indications for the treatment of these infections are the same as in non-rheumatic individuals. Except for the possibility that they may form the focus from which subacute bacterial endocarditis becomes engrafted on a rheumatic valve, there is no reason for washing out a sinus or pulling a tooth that would not be touched in a healthy person. While this possibility is largely theoretical, it should be mentioned that one does occasionally see the development of subacute bacterial endocarditis soon after the extraction of an infected tooth; whether or not this is purely coincidence remains to be determined

Duration of Bed. Rest.—This is often a difficult question to decide. By analogy with other organs, it has been assumed that rest facilitates the healing of an inflammatory process in the heart. However, the situations are not altogether analogous, for the heart muscle can never be put completely at rest Nevertheless, it seems likely that exercise favors dilatation, which is presumably deleterious to the heart muscle. If a patient with rheumatic fever leaves bed soon after the temperature has returned to normal, not uncommonly fever promptly reappears. For these reasons, it is generally considered wise to keep a patient in bed until two or three weeks after rheumatic activity has subsided Among the evidences that rheumatic activity is still present are fever, arthritis, "growing pains," pericarditis, pleurisy, bronchopneumonia, perhaps fresh sore throat, rheumatic eruptions, chorea, fresh subcutaneous nodules, anemia, leukocytosis, acceleration of the sedimentation rate of the red cells, and an electrocardiogram changing toward abnormality. Increase in the severity of the heart failure is usually a manifestation of rheumatic activity in the young On the other hand, the appearance or accentuation of signs of a valvular defect do not necessarily indicate activity; they may result from progressive deformity due to scar formation and may indeed be partially due to the recovery and consequently more powerful action of the myocardium. Of the criteria of activity mentioned, rapid sedimentation time has been considered especially valuable in recent years, for it usually outlasts the others. It should be remembered, however, that heart failure tends to slow the sedimentation rate, so that the acceleration due to activity may be masked if cardiac insufficiency is present; I have repeatedly seen slow sedimentation time in febrile rheumatics who had heart failure. It is known, of course, that even the disappearance of all these clinical criteria of activity does not necessarily mean that the rheumatic inflammation in the heart has completely subsided, for the latter may persist in low-grade form for years and decades, as revealed by the finding at necropsy of Aschoff bodies and even fresh verrucæ. But it is impossible to keep patients

with such low-grade activity in bed. Even following the criteria enumerated it is often necessary to keep the patient in bed for many months and rarely, in children, for as much as a year. Economic conditions often force us to allow a patient with occasional slight fever, joint pains, or especially accelerated sedimentation time to return to his occupation. In the case of children, it is especially important that they be shielded as much as feasible from contact with individuals with respiratory infections, for the latter often initiate a fresh exacerbation of rheumatic activity. However, important as this is, the writer has the impression that in the zeal to eliminate rheumatic infection, children are not uncommonly kept in bed and away from school so long that their education suffers more than is warranted by the improvement obtained by the protracted rest The duration of bed rest and absence from school should be decided for each child individually; the decision is often a difficult one and should be arrived at by a physician and not by a nurse following general rules.

After the patient leaves bed, it is important that his activities be regulated in accord with the functional capacity of the heart. In this regard much has been accomplished for children by means of cardiac classes and homes and for adults by means of social service agencies which aid the individual with heart disease to obtain a position within his working capacity. It is, I believe, true that economically better situated persons with heart disease remain in a compensated stage for a much longer time than do the poor. This is presumably due to the fact that they can take appropriate rest; important, perhaps, is also the environment, for exposure to cold and damp, lack of sunlight, and inadequate diet may well favor reactivation of rheumatic infection. In New York City, one sees little rheumatic disease in the children of the well-to-do and rich, while there is a great deal among the poor.

Climatic Treatment.—It has been found that rheumatic fever is far less common in tropical and subtropical climates than in the temperate zone. Investigations by Faulkner and White,[16] Harrison and Levine,[23] Nichol,[44] and others have shown that the incidence of rheumatic heart disease is far smaller in the Southern states than in the North Thus, Nichol found that in a period of five years, the admission rate of rheumatic fever, rheumatic carditis, and chorea in a general hospital in Miami was only one-tenth that in Boston in the same period. Harrison and Levine's necropsy statistics from New Orleans and Oklahoma City point in the same direction. Because of these facts, many patients with recurring exacerbations of rheumatic activity have been advised to migrate to southern Florida or a similar climate (Porto Rico would probably be well suited if adequate residential facilities were available) in the hope that the rheumatic infection would subside. Whether

the change to the South does actually lessen the incidence of exacerbations in rheumatic individuals enough to make the economically difficult migration worth while remains to be established by observations on large numbers of individuals. But especially in children with recurrent rheumatic activity, the change in climate would, *a priori*, seem well advised.

HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE

The treatment of the cardiac manifestations of hypertension and of coronary arteriosclerosis may be considered together. For in at least the vast majority of instances, cardiac symptoms in hypertension are due to the development of coronary arteriosclerosis, and their management is much the same as when coronary arteriosclerosis develops in the absence of high blood pressure Moreover, such feeble measures as are at our disposal to lower the arterial pressure—bed rest, fluid, salt and dietary restriction, and the use of sedatives—are largely identical with those applied in the treatment of heart failure without hypertension The value of operative procedures on the central nervous sytem for the treatment of hypertension is still not settled and will not be discussed here

From the point of view of treatment, and bearing in mind that they are commonly associated or succeed one another in the same patient, the cardiac disorders engendered by hypertension and coronary arteriosclerosis may be considered in three categories:

1. Angina pectoris.
2. Coronary thrombosis.
3. Heart failure

Angina Pectoris —The following pages are concerned with the treatment of those patients in whom angina pectoris (the term is used purely as a synonym for cardiac pain) dominates the clinical picture. The pain in question is due in the large majority of cases to coronary arteriosclerosis, less often to syphilitic aortitis or rheumatic aortic valvular defects, and rarely to other causes (Chapter XXIII) Unfortunately, at present one can do little more than treat the symptom of cardiac pain, with rarely the possibility of attacking the underlying process.

General Measures.—As most patients learn for themselves, rest is a cardinal measure in the treatment of cardiac pain. Inasmuch as the pain is in all probability due to relative ischemia of the heart muscle, rest tends to avert attacks by diminishing the volume of blood needed by the heart. Many patients have a definite threshold of exercise, *e. g.*, walking so many blocks or climbing so many stairs, above which pain appears In others, excitement is the usual provoking cause of the pain. And even in patients who are subject to nocturnal attacks, the latter are more likely to appear, though

times participate is fall in arterial pressure, thereby lessening the work of the heart But that this is neither the principal nor a constant factor is shown by the observations of Wayne and Laplace[67] who showed that in angina of effort the pressure may return to its previous level before nitrites have afforded relief, and that after relief has been obtained and persists the arterial pressure may return to a higher level than when pain was present. In spontaneous angina, I have repeatedly observed complete relief by nitrites despite little change in blood pressure. Wayne and Laplace describe rare instances of increase in anginal pain due to amyl nitrite, and Wood and Wolferth[72] mention a patient in whom the drug caused preliminary exaggeration with subsequent relief of pain. In such cases, it is likely that the increase in pulse rate, for a time at least, outweighed the factors of coronary dilatation and fall in blood pressure.

As measured by the effect on the blood pressure Wallace and Ringer[65] find the onset and duration of the action of the nitrites in common use to be as follows: Amyl nitrite (by inhalation) acts within ten or fifteen seconds, but the action is over within seven minutes, nitroglycerin starts within a minute, the total duration being about one-half hour; sodium nitrite acts in about five minutes and the blood pressure returns to normal in about an hour or two; erythrol tetranitrate takes about one-half hour to act but the duration of the effect is about five hours.

Nitroglycerin is usually the most useful form of nitrite for the alleviation of an attack of angina pectoris. The drug is most often taken in the form of tablets of $\frac{1}{100}$ grain, which are allowed to dissolve under the tongue or may be swallowed. Sometimes, $\frac{1}{200}$ grain suffices, while others need $\frac{1}{50}$ grain or more. The tablets should be fresh; inert samples are not rare. Or nitroglycerin may be taken in the form of the official 1 per cent alcoholic solution, spirits of glyceryl trinitrate, but this is less convenient. The patient should be instructed to take a tablet whenever he has an attack, and to take another if the first does not bring relief. If certain exercises or excitement which the patient must undertake are known to bring on pain, he should use nitroglycerin as a prophylactic Nitroglycerin taken just before a meal may avert postprandial pain In some individuals nitroglycerin retains its efficacy for years; in others, the relief of pain gradually becomes less and less, which is conceivably due either to habituation to the drug or to advance of the process in the coronary arteries.

The inhalation of amyl nitrite is also widely used for relief of angina. The drug is obtained in pearls containing about 3 minims, which are crushed in a handkerchief. Though amyl nitrite acts even more rapidly than nitroglycerin, the effect is more transitory. While amyl nitrite is rarely needed, some patients state that it is more

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this is not always true, after a strenuous day. For this reason, the patient must learn to keep his activities below the threshold which brings on pain. And if pain comes on during any activity, this should be immediately discontinued until the pain ceases; for if the present conception that the pain bespeaks an ischemic focus in the heart muscle is correct, further activity presumably aggravates the ischemia. Activity includes not only physical exertion but also worry, excitement, etc. Many individuals with pain due to coronary arteriosclerosis get along well for years by appropriate restriction of activities But in prescribing rest the economic status of the individual must be taken into consideration; there is no use ordering protracted confinement to his home for one who cannot leave his occupation.

In some patients with frequent attacks of angina, complete rest brings relief of considerable duration. In several cases with daily attacks, I have obtained excellent results by putting the patient to bed on a diet of less than 1000 calories daily (page 678) with fluid and salt restriction, shielding him as much as feasible from worries, and administering sedatives and coronary dilators. The great value of low-calory diets and small individual meals in angina pectoris has already been discussed (page 677); the rationale is that they diminish the work o' the heart. Of especial importance is loss of body weight by obese patients; not rarely, this diminishes the frequency and severity of the pain, or even abolishes it completely for a time After the patient leaves bed, he is continued on a low-calory diet Such a rigorous "rest cure" is worthy of trial before proceeding to paravertebral block or other more radical measures It is especially apt to be helpful in patients with both high blood pressure and obesity.

The use of tobacco is discussed on page 682. That alcohol is sometimes a valuable therapeutic agent in angina will be mentioned below. Nor is there any general objection to tea and coffee in moderation, although the action of caffein as a coronary dilator is weak. However, as Levy[32] has pointed out, there are rare individuals with or without coronary disease in whom coffee produces cardiac pain; of course, they should abstain.

Recently, Kerr[34] has been able to relieve angina pectoris in certain patients by supporting the abdomen with a specially constructed belt. The typical patient in question "presented a picture of obesity, with a protuberant, pendulous abdomen, exaggerated spinal curves, florid complexion, and poor posture." Kerr thinks that in such patients faulty motion of the diaphragm results in defective venous return to the heart and consequent inadequate coronary flow. Kerr believes that in patients of the type described a properly fitted elastic and supporting belt tends to correct this inadequacy and thus relieve angina. Individuals with a pendulous abdomen are, of course, often

rendered more comfortable by proper abdominal support, but in the few patients with angina due to coronary arteriosclerosis in whom I have seen a supporting belt used there did not seem to be a striking effect on the cardiac pain; perhaps the cases were not properly selected.

Finally, it should be mentioned in conjunction with the general management of patients with angina pectoris that the highly original points of view developed by Libman[36] may lead to notable advances in our understanding of the nature and treatment of the condition. On the basis of thirty-five years of intensive clinical and anatomical observation, Libman has arrived at the "conviction that atherosclerosis and thrombosis of the coronary arteries and 'angina pectoris' of nerve origin are largely of metabolic origin, and that we must stop considering patients from only the standpoint of the heart and arteries They should be regarded as affected by a general disorder, of which the cardiac manifestations are but one evidence" Libman believes that the metabolic disturbance in question is the same as that which underlies so-called gouty states and that disturbance in liver function is concerned. On the basis of this conception, Libman has treated patients with angina pectoris by the administration of calomel, alkalinization by the administration of sodium bicarbonate and other alkalis by mouth and sodium carbonate in enemas, and the rectal implantation of *B. coli*. With this therapy, Libman has succeeded in many cases in diminishing the frequency of anginal pain or even abolishing it for long periods

Nitrites.—These are usually the most helpful remedies for the alleviation of anginal pain other than that due to coronary thrombosis. The nitrites produce vasodilatation, as immediately evidenced by the well-known flush that follows the administration of amyl nitrite or nitroglycerin That the coronary arteries are included in the vasodilatation is shown by the findings that (1) they increase the outflow from the coronary veins both in the intact animal despite fall in aortic pressure (François-Franck,[20] Schloss[51]) and in the excised heart (Smith, Miller and Graber[56]) and (2) they dilate rings of the excised coronary artery (Voegtlin and Macht[64]) Smith[54] found in the dog that if an infarct that was not too large was produced by ligation of a small coronary branch, the injection of nitroglycerin into the left ventricle cleared up the cyanosis of the affected area. On the basis of these findings, it appears highly probable that the efficacy of the nitrites in angina pectoris is due at least predominantly to coronary diltation. It may be that the relief of the relative ischemia of the area which produces the pain may not result from dilatation of the narrowed branch which is principally responsible and which may be so fibrosed and calcified as to be incapable of dilatation, but to an effect on the collaterals like that in Smith's experiments Another factor that may some-

times participate is fall in arterial pressure, thereby lessening the work of the heart. But that this is neither the principal nor a constant factor is shown by the observations of Wayne and Laplace[47] who showed that in angina of effort the pressure may return to its previous level before nitrites have afforded relief, and that after relief has been obtained and persists the arterial pressure may return to a higher level than when pain was present. In spontaneous angina, I have repeatedly observed complete relief by nitrites despite little change in blood pressure. Wayne and Laplace describe rare instances of increase in anginal pain due to amyl nitrite, and Wood and Wolferth[72] mention a patient in whom the drug caused preliminary exaggeration with subsequent relief of pain. In such cases, it is likely that the increase in pulse rate, for a time at least, outweighed the factors of coronary dilatation and fall in blood pressure.

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efficient in relieving their pain than nitroglycerin. Sodium nitrite acts more slowly and is rarely equal to nitroglycerin. Erythrol tetranitrate is so slow in its action that it is useful only for the prevention of attacks, and I have seen so little benefit and so much headache from the drug, which is expensive, that I have abandoned it.

The undesirable side effects of the nitrites are pounding in the head, usually of short duration, and headache, which may be annoying but tends to become less with protracted use of the drugs. There may be faintness, which is less likely to occur when the nitrite is taken in the horizontal posture.

Alcohol.—Spirituous liquors, as known to Heberden, often relieve anginal pain. The effect is presumably due to vasodilatation, although patients are apt to think that they "act on the stomach" and "stop gas." Some obtain quite as good relief, though not so quickly, from whisky as from nitrites. A drink of whisky before retiring may serve as a prophylactic against nocturnal attacks. I have made considerable use of alcohol as a prophylactic of anginal pain in recent years; fears of habituation are scarcely warranted in so serious a disease.

Xanthin Derivatives.—In recent years, various xanthin derivatives have been widely used to lessen the frequency and severity of anginal attacks. The rationale of their use is the production of coronary dilatation in animal experiments. Smith, Miller and Graber[56] found that while caffein sodio-benzoate and theobromine sodio-salicylate (diuretin) had little effect on the rate of perfusion of the coronary arteries of the rabbit, theophyllin, in concentrations estimated to be about those attained in human therapeutics, produced an increase in coronary flow of from 20 to 45 per cent and theophyllin ethylene-diamin (aminophyllin) augmented coronary flow from 40 to 90 per cent Fowler, Hurevitz and Smith[18] have found in the dog that aminophyllin promotes the development of the collateral circulation to a myocardial infarct. Largely on the basis of the earlier of these findings, aminophyllin is now widely used in the treatment of patients with coronary artery disease, having largely displaced theobromin, theobromin calcium salicylate (theocalcin), and other xanthin derivatives. Aminophyllin is prescribed in doses of 0.1 to 0.2 gram, three times daily. Most patients take aminophyllin for months without difficulty, while others develop gastric symptoms. The latter may sometimes be avoided by omitting the drug one or two days weekly. Clinical observations by Marvin,[39] Musser,[45] Smith,[55] Gilbert and Kerr,[21] and Smith, Rathe and Paul[57] indicate that in arteriosclerotic heart disease xanthin derivatives may not only ameliorate anginal pain but also improve the efficiency of the heart. Recently Levy, Bruenn and Williams[33a] have found that aminophyllin prolongs the

time before the appearance of anginal pain induced by anoxemia in individuals with coronary sclerosis. On the other hand, Wayne and Laplace[37] found, in their experiments on the angina of effort, that the administration of aminophyllin by mouth did not improve the exercise tolerance, and did so following intravenous injection in only 2 of 4 subjects and then to a much less extent than did nitroglycerin by mouth. Gold, Kwit and Otto[33] gave 9 to 12 grains of aminophyllin daily to 100 ambulant patients with angina pectoris; they found that this medication had no more effect on the pain than did a placebo. The writer has the impression that although some patients state that they have less pain while taking aminophyllin, the effect is rarely striking and the advantages derived from the long-continued administration of the drug have probably been exaggerated in recent years.

Sedatives.—Many patients with anginal pain are high strung. And even in the placid the use of mild sedatives in the effort to increase the threshold of pain is probably often advantageous. Phenobarbital, chloral and bromide, and even codein when pain is more severe, contribute to the comfort of the patient. In those who are up and about despite occasional anginal pain, the administration of a capsule containing nitroglycerin and phenobarbital after each meal often seems to make the pain less frequent, especially when the latter is postprandial.

Many other varieties of medication have been recommended for angina pectoris, but have not withstood the test of experience. Atropine, especially, has been advocated in various forms and combinations, but, despite the fact that there is good evidence that vagal stimulation constricts the coronary arteries, seems to be of little, if any, value. In recent years, a number of tissue extracts containing vasodilator principles—some of which have been dignified with the title "circulatory hormone"—have been thought to be helpful in angina pectoris. Some of these extracts are prepared from skeletal muscle, others from heart muscle. Another similar extract is prepared from the urine, but the active principle is supposed to be formed by the pancreas. I have seen a number of patients who have been treated with these extracts, some of which are now commercially available in this country, but have not been convinced that they have any value whatever. Such activity as is possessed by at least some of these preparations is due to the presence of cholin derivatives.

Relief of Angina Pectoris by Nerve Section or Paravertebral Block.—In many patients with angina pectoris the "medical measures" just described sooner or later become inefficacious, or are so from the beginning, and there is frequent and severe pain. The suffering may become so atrocious that the patient is willing to undergo any procedure and take any risk as long as they offer some hope for relief of the pain. It is for such patients that measures designed to

block the transmission of painful sensation from the heart to the central nervous system have been attempted. It has been objected to such measures that they remove the "danger signal" which pain constitutes and thus subject the patient to the risk of overexertion with grave consequences. Even if such is the case, it generally constitutes an objection of little moment—at least in the eyes of the patient—for life is intolerable without relief in the type of case for which these measures are designed. Actually, as White[71] points out, most of the patients in whom the previous pain is relieved, have some other equivalent, as mild pain in the opposite side or a sinking sensation which warns them of overexertion This was well exemplified in a young man with the angina of rheumatic aortic regurgitation; his paroxysms of pain were accompanied by sweating, but after paravertebral injection largely relieved the pain the attacks were documented almost solely by the sweating.

The suggestion that angina pectoris might be relieved by interruption of the cervical sympathetic pathways was made in 1891 by the physiologist, François-Franck,[19] as a result of investigations on the sensory functions of the cervical sympathetic It was first carried out in 1916 by Jonesco,[28] who relieved anginal pain by the extensive procedure of bilateral resection of the three cervical and first thoracic sympathetic ganglia Later, Coffey and Brown[8] announced good results in angina pectoris by the much simpler operation of resection of only the superior cervical ganglion. These operations and a variety of others involving resection of sympathetic nerves that could be reached through the neck were quite extensively used. But it soon became evident that, in addition to a not inconsiderable operative mortality in the case of the Jonesco operation, the procedures were efficacious even temporarily in only a fraction of the cases, and in these the pain often returned in a short time Nor were the results obtained by subsequent operators as good as those reported by the originators. The reason for the comparative lack of success of operations on the cervical sympathetic is evident in the light of present knowledge of the course of the sensory fibers from the heart (Levy and Moore[35] and White[71]). In addition to the afferent impulses from the heart that enter the central nervous system through the intermediacy of the cervical sympathetic ganglia, there are also direct *thoracic* cardiac nerves conveying afferent impulses which run from the posterior cardiac plexus to the first to the fifth thoracic ganglia and thence *via* the white rami communicantes and posterior roots into the spinal cord. It is thus evident that no operation on the cervical sympathetic can cut off all the sensory impulses from the heart. A further finding of fundamental importance for the surgical treatment of angina pectoris is that the afferent sensory impulses which travel in the cardiac nerves to the cervical ganglia then pass down the

sympathetic chain to enter the spinal cord *via* the upper five *thoracic* ganglia and their rami communicantes. In other words, *all the sensory impulses will be blocked by interruption of nervous transmission through the upper five thoracic sympathetic ganglia, white rami communicantes, or posterior spinal roots.* As White puts it, these are the focal points through which all cardiac pain must pass Unfortunately, the surgical excision of the upper thoracic ganglia has proven too hazardous in patients with severe coronary artery disease. While White secured nearly perfect relief of pain on the operated side by this operation, 2 of the 4 patients succumbed within a month of the operation.

Much more fortunate results have attended the attempts to block the nervous pathway through the thoracic sympathetic ganglia—so-called paravertebral block—by means of injections. The first substance used was procain, with which Brunn and Mandl[6] obtained relief of anginal pain. A great advance was the introduction of paravertebral block by means of alcohol by Swetlow[60] and Swetlow and Schwartz.[61] The writer had the good fortune to be working at Montefiore Hospital with Drs. Swetlow and Schwartz at the time and witnessing some of the excellent results which they obtained by the procedure. Since then, good results have been obtained by others with Swetlow's method. In 1931, Levy and Moore[35] reported on 49 cases, including 9 of their own. They state that 51 per cent of the patients obtained complete or almost complete relief; improvement was noted in 34 per cent; and in 15 per cent the injection was a failure. The technic has since been further developed by White,[71] to whose monograph the reader is referred for details. In 35 patients with severe angina in whom White carried out paravertebral block, the following results were obtained: 67.7 per cent were 90 to 100 per cent relieved, 17.6 per cent were 50 to 90 per cent relieved, 5 9 per cent were 25 to 50 per cent relieved, 8 8 per cent were failures, and 1 patient who was moribund at the time of injection succumbed. White states that in his last 18 cases there have been no failures. The procedure should have no true operative mortality. The Horner's syndrome that occurs is not sufficiently troublesome to weigh significantly against the operation; the same is true of the sensory disturbances of the chest wall. The most common troublesome complication is painful intercostal neuritis, which may last for months. Injury to the pleura may result in transitory pleuritic pain and rarely pneumothorax or effusion; I recently saw what was probably a peripleural hematoma.

In many of the cases, paravertebral block results in permanent relief of angina; one of White's patients lived for six years without recurrence of left-sided angina pectoris. In some cases, however, in whom there is initial success, the pain later recurs; this may be due to incomplete destruction of the pathways by the injection.

Occasionally, right-sided pain becomes more prominent after left-sided injection stops the pain on the left side.

It should be remembered that paravertebral injection is purely a treatment for cardiac pain, it does not in any way interfere with the usually progressive underlying process. Even though the patients are completely relieved of their pain, coronary thrombosis or other events in the natural history of coronary artery disease may occur, and there is no reason to assume that life is prolonged by the procedure Nevertheless, since paravertebral block relieves the pain in so considerable a percentage of the cases, and since it is attended by so little risk, the procedure is worthy of a trial when angina pectoris fails to yield to purely medical treatment and is so severe as to render life unbearable. It should be remembered that paravertebral block requires a highly developed technic and good results will probably not be obtained by an inexperienced operator. This is presumably the reason that the results reported by White are superior to those of other series and far better than the cases I have seen. Notwithstanding a number of complete failures that I have witnessed, given one who is skilled in the injection, the writer feels on the basis of some comparatively successful cases that he has seen that paravertebral block is a valuable measure in many patients with angina, and will be more widely used than it is at present.

Section of Efferent Fibers.—On the *assumption* that coronary constriction produced by impulses traversing the efferent sympathetic fibers is concerned in the production of the anginal seizure, Raney[48] has recently advocated the treatment of ang'na pectoris by section of efferent preganglionic sympathetic pathways to the heart He does this by extrapleural exposure of the left sympathetic chain from the second to the fifth dorsal ganglia, the corresponding rami communicantes are then sectioned and the sympathetic chain cut between the fifth and sixth dorsal ganglia. By this procedure, Raney obtained complete relief from attacks in the 11 patients on whom he operated I have had no experience with the procedure.

Total Thyroidectomy and Revascularization of the Heart.—These ultimate refuges in the treatment of angina are discussed on page 743 and page 785.

Coronary Thrombosis.—Because of the frequent predominance of shock in the clinical picture, coronary thrombosis presents a therapeutic problem almost unique among the diseases of the heart. In many instances, especially initial attacks in individuals without pre-existent heart failure, it is judicious to treat the victim as a sufferer from shock with only secondary attention, for the time being, to the question of the underlying cardiac failure

Immediate Measures.—Almost always, the patient has already taken to bed by the time the physician arrives. But now and then

one encounters an individual—usually one of the hyposensitives of Libman[37]—with massive myocardial infarction who does not "feel sick enough to go to bed," and requires persuasion. If the condition is critical it may be injudicious to move the patient, unless he is on the street, and sometimes he should not even be disturbed by undressing If the victim is in shock and the extremities are cold, or if there is a chill, he should be kept warm. Many of the patients breathe easily with one pillow, others require to be propped up; when there is syncope due to the cerebral ischemia of shock, this may be counteracted by keeping the head flat. To assure rest, all but the attendants should leave the room and none but indispensable examinations are to be carried out.

In the vast majority of cases, pain is the chief complaint. For this, ¼ grain of morphine sulphate should be administered subcutaneously. If the first injection does not relieve the pain, it should be repeated in twenty minutes. It may be necessary to give a full grain of morphine within a few hours. Enough is to be given to relieve the pain Some advocate initial ½-grain doses but ¼ grain is usually sufficient. It should be remembered that excessive doses of morphine may depress respiration sufficiently to favor pulmonary atelectasis and secondary bronchopneumonia. They may also augment the nausea and vomiting which so often occurs. Morphine not only relieves pain with its pressor reflexes but also dyspnea, if this is present, and secures peace of mind and sleep. Furthermore, there is evidence (Eppinger *et al* [15]) that under the influence of morphine a smaller cardiac output is required, and the resultant diminution in the work of the heart may be of paramount importance.

Nitrites should not be given, They usually have no effect on the pain and the increase in the volume of the vascular bed due to vasodilatation scarcely seems desirable in a state of shock. The slow intravenous injection of 0.5 gram of aminophyllin may relieve pain where morphine has failed. In experimentally produced myocardial infarction in the dog, Smith[57] and his associates found that aminophyllin improves the collateral circulation to the infarcted area.

A measure that is of the utmost value in many cases of coronary thrombosis is the administration of high concentrations of oxygen, the value of which was pointed out especially by Levy and Barach.[38] For patients without a severe clinical picture oxygen is, of course, not required and constitutes a needless expense. But in many critical cases oxygen appears to be life-saving. It is indicated when there is cyanosis or dyspnea and especially in the presence of well-marked congestion or edema of the lungs. Oxygen generally clears up the cyanosis and greatly diminishes or relieves the dyspnea. It often decreases the cardiac pain so that less morphine is needed. Often, the previously restless patient drops off to sleep soon after

being put in the oxygen tent. The pulse may be slower and the other signs of circulatory failure improve The great value of oxygen is often evidenced by reappearance of cyanosis, dyspnea, restlessness, and even pain when the tent is removed. In some cases oxygen is no longer needed after a day or two, while other patients with protracted pulmonary engorgement are best kept in the tent for weeks. The best method for the administration of oxygen in patients with coronary thrombosis, apart from the few institutions with oxygen chambers, is the oxygen tent or mask. If these are not available, the nasal catheter is also of great benefit The concentration of oxygen in the tent should generally be kept about 50 per cent. Future observation may reveal 100 per cent oxygen to be of great value It is especially important in coronary thrombosis that the tent should not be too cold, for this increases the work of the heart.

In the first days of severe coronary thrombosis, the patient should be given only fluids by mouth, administered very slowly by the nurse If orange juice or milk increase abdominal distention, as they sometimes do, they should be discontinued. Because of the profuse sweating, fever, and perhaps vomiting, the thirst of the patient may be so great that considerable amounts of fluid are needed. But on the principle of avoiding as much activity as possible, the smallest amount of fluid feasible should be given in the first days of major attacks. In some cases vomiting due to the cardiac lesion or to morphine makes it difficult to give fluid by mouth. If the vomiting persists, physiological solution of sodium chloride may have to be given under the skin with as little disturbance to the patient as possible Large intravenous infusions would seem to be contraindicated because of the danger of pulmonary edema. A rectal drip is usually unsuccessful

The morphine generally results in constipation. It is well that the patient should not be disturbed to move his bowels during the first two or three days, especially if distention does not develop, straining at stool is dangerous. After the third day a small enema or low irrigation may be given, but it should be carried out with the least possible disturbance to the patient, fatal collapse during an enema occurred in a patient who previously seemed to be doing well. After the first few days, mild laxatives are usually advisable

Distention is often a troublesome symptom in coronary thrombosis, it may be partially due to morphine, but also occurs without the latter, perhaps as a result of a reflex from the heart. A rectal tube may afford some relief. If not, small enemas with turpentine may be attempted cautiously. I have seen pituitrin and prostigmin used successfully for the tympanites of coronary thrombosis, but this would appear to be dangerous because of the pressor effect

Embolization of mural thrombi from the endocardial surface of the infarct constitutes a danger in the second and third weeks against

which the physician has been helpless. Best[4] has suggested that the intravenous administration of heparin may prevent the formation of such mural thrombi and the extension of the vascular thrombosis. The value of this procedure remains to be demonstrated.

Early Emergencies.—Certain emergencies may occur at any time from the very onset of coronary thrombosis. Of these the most common is *profound shock;* the cyanosis becomes ashy, the pulse thready or imperceptible, the systolic blood pressure falls below 80 mm., and death from inadequate cardiac output seems imminent. The most useful remedy in such critical situations is epinephrin, of which 0.5 or 0.75 mg. may be injected subcutaneously. On several occasions I have seen individuals apparently succumbing to the shock of coronary thrombosis with impalpable pulse and blood pressure not obtainable promptly respond to the injection of epinephrin and survive the attack. In less critical situations, coramine or caffein sodio-benzoate may be given subcutaneously or intramuscularly, or 3 cc. of coramine may be injected intravenously or intramuscularly. Marvin[46] and others have administered hypertonic glucose solution (50 or 100 cc. of a 50 per cent solution) intravenously in coronary thrombosis with good results. These findings harmonize with the demonstration by Ginsberg[22] and his associates that the intravenous injection into the intact dog of 50 per cent glucose solution is followed by a marked and sustained augmentation of coronary blood flow. It has also been assumed, without proof, that the sugar improves the nutrition of the ischemic heart muscle. On the other hand, the injection of the hypertonic solution draws fluid into the blood stream and thus increases the work of the heart. Ellis and Faulkner[14] found that the injection of 100 cc. of 50 per cent dextrose in ten minutes caused an average rise of 13 per cent in circulating blood volume, which started to return toward normal in thirty minutes. Such increase in blood volume augments the work of the heart. In accord with this, Scherf and Weissberg[59] found that injection of 50 cc. of 50 per cent dextrose into patients with angina due to coronary sclerosis was followed by marked electrocardiographic changes (depression of *T* wave and *S-T* interval) and frequently evoked cardiac pain; these effects were not observed in normal controls. I have twice seen violent paroxysmal dyspnea follow hypertonic glucose injections in myocardial infarction. In the light of these observations it would seem that great caution should be observed in the injection of hypertonic solutions in myocardial infarction, and they should be confined to patients in profound shock or with menacing pulmonary edema.

Another emergency that arises on rare occasions at the very onset of coronary thrombosis is *fulminant pulmonary edema* due to left ventricular failure. The patient may succumb before the physician arrives. If not, venesection may prove life-saving. An

intravenous injection of hypertonic glucose or dextrose solution may be of value.

Ventricular tachycardia occurs in rare cases of coronary thrombosis and is very dangerous There is sudden acceleration in the rate of the heart. According to Levine,[31] who has studied this disturbance in mechanism in special detail, ventricular tachycardia is characterized by a rate usually between 160 and 220 per minute in which, while the rhythm is for the most part regular, there are occasional slight interruptions which are accompanied by variations in the intensity and quality of the first sound; the rate is uninfluenced by ocular or carotid sinus pressure. Levine has found that the administration of quinidine sulphate generally abolishes the ventricular tachycardia of coronary thrombosis with restoration of regular rhythm; the doses he required varied between 0.3 and more than 1 gram, starting with the small dose and repeating with a larger one every four hours. Since reading Levine's report, I have also observed the abolition of ventricular tachycardia in coronary thrombosis following the administration of quinidine, but have failed with the drug in two other cases, perhaps because the maximum dose recommended by him was not given. Levine has recommended the routine administration in coronary thrombosis of 0.2 gram of quinidine sulphate three times daily for two weeks as a prophylactic of ventricular tachycardia and fibrillation and auricular fibrillation. *Auriculo-ventricular block* with Stokes-Adams syndrome is a rare complication of thrombosis of the right coronary artery with infarction of the posterior portion of the septum. Since the syncopal attacks are dangerous, the attempts should be made to accelerate the ventricular rate by the subcutaneous injection of 0 5 or 0 75 mg. of epinephrin This may be repeated several times if the ventricular rate again falls *Auricular fibrillation* or *flutter* may develop during the first days of coronary thrombosis, but are most often paroxysmal, for which reason quinidine and not digitalis is usually advisable.

Digitalis.—The question of the use of digitalis in the first days of coronary thrombosis is a moot one. At present, most physicians do not use it. In patients with an initial attack of coronary thrombosis occurring in a heart that was previously functionally competent, digitalis does not seem indicated For in these patients the clinical picture is dominated by shock, and further decrease in circulating blood volume due to digitalis (page 709) is probably not desirable. Moreover, digitalis carries with it conceivable dangers, namely, detachment of parietal thrombi with embolization, rupture of the heart as a result of more forceful contraction, and ventricular tachycardia or fibrillation as a result of greater irritability of the ventricular muscle. Whether digitalis really does have these untoward effects is difficult to demonstrate, for all of them may also

occur when the drug is not administered. A well-grounded indication for digitalis occurs only when coronary thrombosis results in a clinical picture dominated by heart failure with intense pulmonary engorgement, marked swelling of the cervical veins and liver, and edema. This is most often the case when the occlusion occurs in a heart that was previously functionally impaired. Digitalis is also indicated in the rare cases in which there is continuous auricular fibrillation with heart failure. In such patients I have repeatedly observed prompt improvement follow digitalization with moderate doses. But I have been unable to decide whether the advantages of digitalis in such cases outweigh the possible risks.

Insulin.—A considerable proportion of cases of coronary thrombosis occurs in diabetics. It is to be strongly emphasized that *one should be exceedingly circumspect with the administration of insulin in such patients*. In Chapter XXIX it has been seen that insulin hypoglycemia increases the work of the heart, and that the injection of insulin may be followed in individuals with coronary arteriosclerosis by anginal pain and perhaps coronary thrombosis. Severe intensification of the symptoms of coronary thrombosis may follow the injection of insulin; these may go on to a fatal outcome. Unless, therefore, progressive ketosis necessitates insulin, it should be omitted in individuals with coronary thrombosis. If insulin must be given, it should be covered with glucose by a very large margin, no matter how great the glycosuria, so that there is no possibility of hypoglycemia. In fact, I always endeavor to maintain a hyperglycemia in the early phases of coronary thrombosis.

Later Management.—Following the acute stage of coronary thrombosis, the patient must be kept in bed for a protracted period. This apparently aids in the formation of a strong and small scar. Sultan and Davis[59] found that following the production of myocardial infarction in dogs, rest resulted in the development of a small, firm scar, while exercise resulted in a thin, bulging scar. The postmortem observations of Mallory, White and Salcedo-Salgar[33] indicated that small infarcts are almost completely healed after five weeks, while large infarcts are completely healed or undergo no further change after two months. A long rest is probably the more important the younger the individual and the better the outcome, for we know now that such persons may have many years of happiness and economic usefulness after even severe myocardial infarction. While the length of bed rest varies in individual cases, it should hardly be less than a month, even with what seem to be small infarcts. With large infarcts a longer duration of bed rest, six weeks or two months, is desirable even though the patient is asymptomatic. During this period the patient is advantageously kept on a low-calory diet with fluid and salt restriction (Chapter XXXIII); Master[41] has especially emphasized the

excellent results to be obtained by such a régime. If the patient is obese, advantage should be taken of the opportunity to obtain appropriate reduction in body weight. If symptoms of heart failure are present, the patient is to be treated according to the general principles for the management of cardiac insufficiency detailed in previous chapters. After the first two or three weeks the possible contraindications to the use of digitalis during the acute phase no longer apply and the drug is often very valuable. Mercurial diuretics may also be exceedingly useful in heart failure following coronary thrombosis

Treatment of Heart Failure in Hypertensive and Arteriosclerotic Heart Disease.—The treatment of patients with heart failure due to coronary arteriosclerosis with or without hypertension is largely symptomatic. We do not have at our disposal means for the elimination of the underlying hypertension or coronary arteriosclerosis, and can do no more than treat the cardiac insufficiency in accord with the general principles of the treatment of heart failure already outlined. By the judicious use of bed rest, fluid, salt and caloric restriction, and the administration of mercurial diuretics and digitalis, excellent results are often attained, and an individual incapacitated by dyspnea, edema, and the other consequences of heart failure may be restored to economic usefulness for often considerable periods of time. Details regarding the application of these therapeutic measures have been given in previous chapters. A few words will be added, however, regarding the treatment of left ventricular failure, which occurs in uncomplicated form most commonly in hypertensive and arteriosclerotic heart disease.

Treatment of Isolated Left Ventricular Failure.—A great many patients with coronary arteriosclerosis or hypertension first present themselves with and because of left ventricular failure The chief complaint is usually dyspnea, which may be either exertional or in the form of nocturnal paroxysms of cardiac asthma. Examination may reveal evidences of pulmonary engorgement but systemic venous engorgement and its consequences are absent. Therapeutically, a great deal can be done for these patients. If their circumstances permit, they should be put to bed for a week or two. A low-calory diet with fluid and salt restriction should be advised. In fact, perhaps the most generally efficacious method of treatment is to keep the patient on a Karell diet for two or three days at the start. On this régime alone, great improvement is frequently noted, especially if the patient is obese and loses considerable weight. It is in hypertensive and arteriosclerotic heart disease that reduction of body weight is most often of help in alleviating cardiac failure. However, in addition to these measures the administration of digitalis is often of great value. This has not always been realized

because the patients in question have regular rhythm and tachycardia is rarely marked. Moreover, the unjustified apprehension of the administration of digitalis in hypertension (page 710) and in the presence of coronary arteriosclerosis (page 729) has resulted in the withholding of digitalis from many of these patients. In recent years, however, it has been quite generally realized that digitalis is often of great value in left ventricular failure due to hypertension and coronary arteriosclerosis. In a careful study of ambulant patients of this type attending a dispensary, Harrison[14] and his co-workers were able to show that dyspnea was greatly ameliorated by the exhibition of digitalis. I have had the same experience on numerous occasions Many individuals incapacitated from their occupation by exertional dyspnea are enabled to return to it by the administration of digitalis Attacks of cardiac asthma may also be diminished in frequency or abolished by digitalis. Some patients with left ventricular strain due to hypertension and coronary arteriosclerosis take digitalis for years; cessation of the drug is followed by augmentation of dyspnea.

Cardiac Asthma and Acute Pulmonary Edema.—These manifestations of left ventricular failure may constitute difficult therapeutic problems. As mentioned in the preceding paragraph, bed rest, fluid and salt restriction, and the administration of digitalis are often followed by alleviation of cardiac asthma. Patients who are subject to paroxysmal nocturnal dyspnea should have a light supper with little fluid and refrain from eating or drinking after it; this simple measure sometimes relieves cardiac asthma. The patient should sleep propped up; some sufferers state that their attacks come on if they slip down Codein before retiring may also be helpful. Following diuresis produced by mercupurin or salyrgan, the patient may be free of cardiac asthma for a time; it would appear that all measures which dehydrate the body militate against paroxysmal dyspnea If the physician is called during the attack, the injection of morphine is usually efficacious and the patient drops off to sleep. The intramuscular or intravenous injection of 3 cc of coramine may be of notable help in the treatment of paroxysmal dyspnea.

If the paroxysm of dyspnea is accompanied by manifest pulmonary edema, the situation is serious, although many patients survive repeated attacks of even massive pulmonary edema. The first thing to be done is the administration of ¼ grain of morphine. This is often spectacularly helpful; the dyspnea, cough and expectoration cease and the râles gradually disappear. Why morphine is so often helpful in cardiac asthma and pulmonary edema remains to be explained; there is some evidence that the narcotic decreases the venous return to the heart, which would tend to relieve the overloading of the pulmonary circuit that is so important in the

genesis of the attack. If morphine fails, venesection should be carried out and is sometimes life-saving. If the patient is cyanotic and oxygen is available, it should be administered; I have seen the cyanosis clear up after a few minutes in the oxygen tent. If the patient has not received digitalis, the intravenous injection of strophanthin or digitalis would seem called for to overcome the insufficiency of the left ventricle. Good results have been reported from the use of these glucosides and I have made what seemed to be similar observations with the intravenous injection of digitalis, but it is difficult to be sure of the therapeutic utility of a measure in pulmonary edema, in which spontaneous sudden turns for better or worse are common. Barach, Martin and Eckman[1] have seen prompt clearing up of pulmonary edema as a result of positive pressure respiration.

Cheyne-Stokes Breathing.—This occurs most commonly in patients with hypertensive and arteriosclerotic heart disease in its terminal phases. The breathing can usually be rendered regular for a time by the inhalation of carbon dioxide, oxygen tends to diminish the intensity of the apneic and dyspneic phases but rarely renders the breathing completely uniform. As pointed out by Vogl,[65] the intravenous injection of 0.24 gram of aminophyllin often abolishes Cheyne-Stokes breathing for a time, although in other cases it fails completely. However, even if one can abolish Cheyne-Stokes breathing by any of these procedures, it is hardly of aid to the patient.

Surgical Treatment of Arteriosclerotic Heart Disease.—The value of thyroidectomy in arteriosclerotic heart disease is discussed in Chapter XXXV.

Recently, Beck[2] has introduced a surgical treatment of arteriosclerotic heart disease, including cases in which myocardial infarction has occurred, along new lines. The underlying principle of Beck's extremely interesting work is the development of a collateral circulation to the myocardium by the production of adhesions between the heart muscle and the parietal pericardium and the pectoralis major muscle. He has shown that the resulting collateral circulation functions to reduce the myocardial ischemia produced in dogs by coronary obstruction. With this experimental basis, Beck has carried out his operation on a considerable number of patients with arteriosclerotic heart disease. O'Shaughnessy[11] has attempted to attain the same end—revascularization of the heart—by grafting the omentum onto the heart—cardio-omentopexy.

Feil and Beck[17] reported their results in 25 patients with arteriosclerotic heart disease producing intractable angina pectoris. Half of the first 12 patients operated succumbed, while in the last 13, after modification of the operation, the mortality was reduced to 15.4 per cent; the last 9 operations were without mortality. Feil and

Beck state that all of the 13 patients observed for five months or longer after the operation were improved. Three of the results exceeded their expectations; one of these patients, who had suffered from angina for nine years, was asymptomatic on even considerable exertion two and a half years after operation. O'Shaughnessy and his associates report 5 deaths in 20 patients on whom they operated; all the others were improved six months or more after the operation and most of them were free from symptoms.

The first results of Beck's ingenious and theoretically well founded procedure would thus appear very promising. However, further observations with this type of operation, with which the writer has no personal experience, must be awaited before its actual value can be assessed. At present, the operation hardly comes into consideration except in patients with angina due to coronary arteriosclerosis in whom life under the customary methods of treatment has become intolerable. Peculiarly enough, Feil and Beck observed improvement in his patients within eight or ten days; since this is too short an interval for significant revascularization, interruption of subepicardial nerves may be concerned.

SYPHILITIC HEART DISEASE

Patients with heart failure or angina pectoris due to syphilitic heart disease should, of course, receive the general treatment for cardiac insufficiency or pain already outlined. But in addition—or alone if heart failure or angina are absent—specific antisyphilitic treatment comes into question. The value of antiluetic treatment in syphilitic aortitis and its complications has been variously assessed in the past Soon after the introduction of the arsenicals, doses of old arsphenamine and then of neoarsphenamine were given which are now known to have been too large. The result was frequent severe reactions and even some fatalities due to rupture of the aorta, Herxheimer reactions, and other causes. In consequence, until the past few years, many physicians considered the arsenical dangerous in luetic heart disease, and other forms of treatment were given in dosage so small as to be of little utility. In recent years, however, it has been shown that adequate antisyphilitic treatment notably improves the grave prognosis of luetic heart disease and that it carries little risk when affected with appropriate caution. This point of view has been especially fortified by the excellent studies on large material of Moore and Metildie[44] and the collective investigation at various clinics (10,614 patients) brought together by Cole and Usilton.[9]

These investigations have established that cardiovascular syphilis rarely develops in individuals who have been adequately treated in the early stages of the disease. In fact, Cole and Usilton found

that "among the patients who were followed from three to twenty years, none of the graver forms of cardiovascular syphilis developed if treatment had been adequate during the early stages of syphilis." The conclusive evidence of the great value of adequate antisyphilitic treatment after the detection of cardiovascular lues brought forward in the collective investigation summarized by Cole and Usilton is as follows.

Uncomplicated Syphilitic Aortitis.—The average duration of life of patients who died was thirty-four months with inadequate treatment and eighty-five months with adequate treatment. Of those inadequately treated, 49 per cent were living and free from symptoms as compared with 63 per cent of those adequately treated. Cardiovascular lues was the probable cause of death in 7.9 per cent of those inadequately treated and in 2 4 per cent of those adequately treated.

Syphilitic Aortitis With Aortic Regurgitation.—Adequate treatment after the discovery of the leak increased the average duration of life to fifty-five months from the forty months of those inadequately treated. Symptomatic relief was obtained in 60 per cent of those given adequate treatment and in only 30 per cent of those given inadequate treatment.

Syphilitic Aortitis With Saccular Aneurysm —Those patients who were given large doses of both an arsenical and a heavy metal after the detection of the aneurysm had an average duration of life of seventy-five months, while those who had but small doses had an average duration of life of only thirty-seven months

In the light of these facts, the value of specific treatment, including arsenicals, in syphilitic heart disease would appear to be established. However, it cannot be too strongly emphasized that one must proceed cautiously, else serious reactions and even fatalities will be encountered. Caution is especially important in patients with anginal pains, in whom too intensive treatment may be followed by exacerbation of the pain, violent dyspnea, or even pulmonary edema, some such attacks may be due to edema or engorgement of the aortic wall further narrowing a coronary orifice already impinged upon Or Herxheimer reactions may occur That rupture of the aorta has been known to follow large doses of old arsphenamine was already mentioned Following too intensive treatment, Wile[68] observed what he termed a "therapeutic paradox," *i. e.*, temporary improvement followed by aggravation, which he attributed to distortion of the aortic cusps and wall due to rapid changes

If the patient with luetic aortitis has heart failure, it is probably wiser to endeavor to restore compensation by means of bed rest, fluid and salt restriction, digitalis, diuretics, etc., before starting specific treatment. The latter should be initiated by six or eight weeks of bismuth or mercury and potassium iodide, starting with

small doses. Neoarsphenamine should then be started with a dose of 0.05 gram, gradually increasing with weekly injections to a maximum of about 0.3 or 0.4 gram. A course of about 15 injections of neoarsphenamine may be alternated with a course of heavy metal. How long the treatment is to be continued must be decided in accord with the course of events in the individual case; for details, the reader is referred to the publications of Moore[43] and Cole and Usilton.[9] The small danger of reaction when one is cautious is indicated by the statistics collected by Cole and Usilton, which show that in 5313 injections of arsenicals there were only 12 severe reactions, i. e., 2.25 per 1000 injections

HYPERTHYROIDISM

The operative treatment of heart failure due to hyperthyroidism is the most satisfactory chapter in the treatment of cardiac insufficiency. This is due to the fact that subtotal thyroidectomy removes the cause of the heart failure—an objective rarely attained in the treatment of any of the other common forms of heart disease Even when heart failure is very severe with intense dyspnea, massive edema and transudates in the serous cavities, operation is often followed by prompt and lasting improvement with economic rehabilitation. In the frequent cases in which hyperthyroidism is associated with essential hypertension, coronary arteriosclerosis, or valvular defects in the causation of the heart failure, the removal of the hyperthyroidism generally results in considerable improvement Because of the splendid therapeutic results, it is important that the physicians keep close watch for the participation of an element of hyperthyroidism in obscure cases of cardiac insufficiency. Heart failure may result from hyperthyroidism in the absence of exophthalmus, psychomotor unrest, and the other classical manifestations of Graves' disease (Chapter XXVIII). Especially auricular fibrillation of obscure genesis is to be suspected of hyperthyroid origin and the metabolic rate determined.

Operation is almost always indicated for heart disease due to hyperthyroidism. It is true that one can generally attain considerable improvement by bed rest, the administration of iodine, and, in patients with auricular fibrillation or heart failure, digitalization. But this improvement is rarely lasting. The same is true of irradiation of the thyroid gland The number of thyrocardiacs, as Lahey[29] calls them, whose condition does not permit operation is very small. Even those with extreme heart failure can usually be brought into a condition in which the risks of operation are relatively slight. The small operative danger and excellent results in competent hands are exemplified by the following statistics of Lahey:[29] Of 120 thyrocardiacs, 5 died during the operation and 14 subse-

quently. Of the 101 alive, 76 had full return of the function enjoyed before the onset of hyperthyroidism, 19 remained with persistent auricular fibrillation, 4 were partially disabled, and 9 completely disabled. Similar results have been obtained in the cases operated upon at Mount Sinai Hospital. Restitution of compensation often occurs within a few days after operation.

Most important is the judicious preparation of the thyrocardiac for operation. The patient is to be kept at complete bed rest in a quiet room with avoidance of unpleasant news and exciting company, and Lugol's solution administered in doses of 10 minims three times a day These measures generally effect considerable improvement of the circulation. Without iodine, when the metabolic rate is high, digitalis is generally of little or no avail and rarely slows the ventricular rate much despite the fact that the majority of the cases have auricular fibrillation. But digitalis is a valuable adjuvant to iodine in the pre-operative preparation of patients with auricular fibrillation or heart failure. This is often demonstrated by further slowing of the pulse when a previously iodinized patient is given digitalis. The pre-operative digitalization of all patients with auricular fibrillation or heart failure thus seems advisable. Needless to say, the fluid and sodium chloride intake of the patient with heart failure of thyrotoxic origin should be restricted as in other forms of cardiac insufficiency. But since most of the patients have lost weight, and the metabolic rate is elevated, the caloric value of the diet should be high and the protein ration adequate to prevent a negative nitrogen balance and permit the replacement of body protein that has previously been burned. If there is edema, mercurial diuretics may be valuable. But in view of the importance of dehydration in the pathogenesis of surgical shock, one should be careful not to cause too great a loss of fluid and salt, this is especially to be feared in hyperthyroidism where perspiration may be profuse Adequate sedation with chloral and bromide, phenolbarbital, etc., is particularly important in the thyrocardiac patient

Prior to operation, the administration of quinidine to patients with auricular fibrillation is generally inadvisable, it rarely restores normal rhythm and may cause toxic reactions. In a considerable proportion of the cases, sinus rhythm returns spontaneously within a few days after operation If the rhythm does not become normal within a week after operation, quinidine should be administered (page 752), and is often successful. The operation sometimes precipitates auricular fibrillation, but this is usually transient.

General anesthesia does not seem to add to the risk of the operation and is usually preferable. Most often, subtotal thyroidectomy can be performed in a single operation, but occasionally a two-stage operation is judicious Lahey advises that the more severely ill

thyrocardiacs be anesthetized and operated upon in the upright position. For these and other surgical details, the reader is referred to the papers of Lahey.[28]

CIRCULATORY FAILURE IN DIPHTHERIA

The chief danger to life in diphtheria is circulatory failure. In the vast majority of instances, this can be forestalled by the early and adequate injection of antitoxin. However, the protection is not absolute; on rare occasions, fatal circulatory failure has occurred despite enormous doses of antitoxin on the first day. Precautions against circulatory failure should therefore be taken even though antitoxin has been given. It seems probable that myocarditis occurs in almost all, if not all, severe cases of diphtheria, and is especially likely to be severe in patients with nervous or renal involvement Cardiac implication probably also takes place in a considerable percentage of seemingly mild cases of diphtheria. For this reason, it seems wise even in mild cases to keep the child recumbent in bed for a week after the membrane has cleared; in severe infections the rest should be longer and any abrupt movement avoided The occurrence of vomiting may forewarn of circulatory failure and calls for absolute rest in the recumbent posture If the patients are carefully watched, death from circulatory failure will seldom come as a complete surprise. Significant myocardial lesions in diphtheria are almost always documented in the electrocardiogram; such a tracing should be made, if feasible, and protracted, rest enforced if changes are present.

Once circulatory failure has set in, the results of treatment are most often not striking and the mortality is high. This is perhaps due in some part to the fact that both cardiac and peripheral circulatory failure are present. The principal reason, however, is that the severity of the myocardial damage in diphtheria is rarely duplicated in other circumstances The administration of digitalis comes into question only in patients with swelling of the liver and other evidences of severe heart failure, and even here the desirability of the glucosides is more than doubtful. Although it has been claimed that digitalis has some protecting effect against diphtheria toxin in the guinea-pig, this has not been found to be the case in the cat and dog. Likewise, while some pediatricians of wide experience find that digitalis is of striking benefit in many instances of diphtheritic myocarditis, others have the contrary experience. In view of the frequency with which diphtheritic heart disease is manifested by intraventricular, bundle-branch, or auriculo-ventricular block, the administration of digitalis calls for great caution. The experimental observations of Edmunds[13] and his associates indicate that digitalis may readily aggravate block in the diphtheria heart. The

administration of hypertonic glucose solution has been reported to yield excellent results in the circulatory failure of diphtheria; while the solution has been thought to affect favorably the myocardial disease, it seems plausible that the chief value is to combat the element of peripheral circulatory failure. On the basis of the theory that damage to the adrenal cortex is concerned in the circulatory failure of diphtheria, the injection of cortical extract has been recommended and good results reported, but further evidence is required before the efficacy of this treatment can be accepted

ADHESIVE MEDIASTINO-PERICARDITIS AND CONSTRICTIVE PERICARDITIS

In the vast majority of these cases, the therapeutic procedures that help in other forms of heart failure are of little or no utility Usually, despite bed rest, fluid and salt restriction, diuretics, and digitalis, ascites accumulates and one must resort to repeated paracentesis of the abdomen.

In recent years, the entire outlook has been changed by the development of the surgical treatment of the conditions. Depending on the nature of the pericardial lesions, two types of operation are carried out:

1. Resection of the precordial portions of several ribs, the so-called cardiolysis of Brauer.[5] This operation may be of considerable aid in the rare cases in which mediastino-pericarditis results in firm adhesions of the heart to the chest wall so that with each systole the heart must pull in the bony thorax and thus perform greatly increased work. In these cases the heart is enormous and pronounced systolic retractions are present. The resection of the ribs diminishes the work necessary to pull in the chest wall with each systole and thus tends to help the heart failure. It is to be repeated that cases of this type, and consequently the indications for the Brauer operation, are *extremely* rare.

2. Resection of as much as feasible of the thickened and sometimes calcified pericardium, decortication of the heart, an operation suggested by Delorme [12] This operation is indicated in constrictive pericarditis, *i e.*, the condition in which thickening and shrinking of the pericardium results in compression of the heart with limitation in the amplitude of diastole and sometimes constriction of the great veins. In these patients the heart is characteristically not much enlarged; indeed, the cardiac silhouette may appear small. Constrictive pericarditis, and consequently the indication for the Delorme operation, is much less rare than is the preceding group of cases. In skilled hands, the results of the operative treatment of constrictive pericarditis have been excellent, especially when viewed in the light of the previously hopeless prognosis Thus, of 10 cases

studied by White[70] and operated on by Churchill, 6 were completely cured and 1 relieved to a high degree. However, it must be remembered that the procedure has an operative mortality, and that it should be done only by a highly skilful surgeon. For details concerning the operation, the reader is referred to the publications of Beck[3] and White.[70]

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CHAPTER XXXVIII

TREATMENT OF PERIPHERAL CIRCULATORY FAILURE AND SHOCK

In Chapter XXXII it has been seen that the common denominator of the different forms of peripheral circulatory failure is a deficient venous return to the heart. The cutting down of the venous return apparently most often results from decrease in the ratio of the volume of blood in active circulation to the capacity of the vascular bed, due to either diminution in the former or increase in the latter. In the effort to rectify this disproportion, two obvious paths have been pursued:

1 The administration of fluids designed to augment the volume of blood in active circulation.

2. The exhibition of vasoconstrictor drugs in the effort to diminish the capacity of the vascular bed.

THE ADMINISTRATION OF FLUIDS

The administration of fluids is almost always called for in shock and yields splendid results in many forms. This is especially true since the technic of slow and protracted intravenous infusion—phleboclysis or intravenous drip—has been developed. The primary objectives in the treatment of shock by the administration of fluids are as follows:

1. To increase the volume of blood in active circulation. This may be accomplished by the direct or indirect introduction of fluid into the blood stream, or by the injection of hypertonic or colloidal solutions into the blood, which, through their osmotic pressure, draw tissue fluid into the circulation. A further desideratum is that the increase in circulating blood volume thus attained be maintained. This is important, though often difficult to achieve, because the mechanisms which originally produced the decrease in circulating blood volume continue to operate.

2. To alleviate dehydration of the tissues. The three great fluid compartments of the body—the circulating plasma, the intercellular fluid, and the intracellular fluid—communicate with one another, and changes in any one may influence the others. Often, very large volumes of fluid are required to replenish the lost water content of the cells and the intercellular spaces.

3. To replenish salts which have been lost; the fluid administered serves as a vehicle for the electrolytes in question. Most often, dehydration and diminished blood volume are secondary to loss of

electrolyte, and water can be fixed in the organism only if the necessary skeleton of electrolytes is built up. How large a quantity of salts may be required is indicated by Darrow's[11] estimate that in marked dehydration about one third of the extracellular electrolyte is lost.

4. To rectify the biochemical disturbances which are usually present, notably those in which change in the composition of the blood is concerned. For example, in hemorrhagic shock transfusion of blood is superior to infusion of salt solution because, among other reasons, it augments the decreased oxygen-carrying capacity of the blood. Similarly, in the circulatory collapse of diabetic acidosis the infusion of base tends to correct the disturbance in acid-base equilibrium.

5 To furnish food by means of glucose infusions where an undernourished individual can take it by no other route. However, it is to be emphasized that only very exceptionally is the caloric value of a glucose infusion a significant consideration, although its antiketogenic and protein-sparing properties, as well as the protection of the liver through replenishment of an exhausted glycogen reserve, may be important.

The principal forms of fluid which are used to attain these objectives are the following:

Blood.—Transfusion of blood has long been recognized as a valuable measure in the treatment of shock In hemorrhagic shock, of course, the indication for transfusion and the rationale of its usual success if the bleeding stops are obvious In forms of shock other than that due to hemorrhage, transfusion likewise often results in prompt improvement, including rise in the depressed blood pressure. The beneficial effects of blood transfusion in shock in which there is no decrease in the red cell count is doubtless due to increase in circulating blood volume. However, in many forms of peripheral circulatory failure due to dehydration and salt depletion (vomiting, diabetic acidosis, etc.), it is usually impossible to transfuse enough blood to alleviate the dehydration and salt deficiency. In such cases, while transfusion may be a valuable adjuvant, the principal part in restoring the fluid and salt content of the organism is accomplished by the administration of the saline solutions to be mentioned in the following paragraphs. Salt solutions or plasma rather than blood are called for especially in those cases in which dehydration has resulted in an increase in the red cell count (and sometimes in the concentration of plasma protein), for in these cases the decrease in circulating blood volume is due entirely to diminution in plasma volume

Human Serum.—Most forms of oligemic shock, including massive hemorrhage, are due almost entirely to decrease in blood volume and little or not at all to decrease in the oxygen-carrying capacity of the

blood. It might therefore be anticipated that human plasma or serum would function almost as well as whole blood in the immediate treatment of oligemic shock. Recently, Levinson[20] and his associates have shown that this is actually the case. They produced secondary shock in dogs by repeated bleeding and found that the intravenous injection of blood serum relieved the shock practically as well as whole blood and far better than crystalloidal solutions. In a few instances of shock in humans, Levinson *et al*, obtained excellent results paralleling those in the animal experiments. Because typing is not needed and because of the ease of storage and handling, it would seem likely that infusions of serum will have a large place in the emergency treatment of shock, particularly in war. Human serum concentrated by the lyophile process (vacuum dehydration at low temperature), which is available as a powder, may prove to be especially useful in treating hemorrhagic and other forms of shock in the emergencies of war. Unfortunately, it is expensive.

Sodium Chloride Solutions.—In most forms of peripheral circulatory failure with shock, the administration of sodium chloride solution is a valuable measure. This is especially true where dehydration has occurred. Under these circumstances, the salt solution tends rapidly to leave the blood stream and replenish the water content of the exsiccated tissues and after this has been accomplished to augment the circulating blood volume—the desired objectives in shock due to dehydration. As has been seen in Chapter XXXII, in some of the common forms of shock dehydration is secondary to depletion of the electrolytes, especially of the fixed base, of the organism; the administration of sodium chloride tends to remedy this deficiency.

Patients in shock rarely can take fluids by mouth or rectum. For this reason sodium chloride solution is generally administered to such individuals either subcutaneously or intravenously; to infants, it is sometimes given intraperitoneally. When the circulation is deeply depressed, absorption from the subcutaneous tissues is poor and the intravenous route must be used. The solution is most often given in the form of physiological or isotonic (0.85 per cent) solution of sodium chloride. The amount of solution and speed of intravenous injection vary with the circumstances. In grave emergencies with very low or unobtainable blood pressure, 1 liter of salt solution may be given intravenously at a rate of about 30 cc. per minute, carefully watching the pulse and blood pressure, and slowing the rate of infusion when these improve. Other than in pressing emergencies the intravenous infusion should be given slowly, the drip being arranged so that between 250 and 500 cc. per hour are delivered. By such slow infusions, one can often advantageously give dehydrated individuals as much as 3000 or even 4000 cc. daily.

When these large intravenous infusions are administered, the pulse and blood pressure should be watched carefully, the lungs examined at intervals for evidences of pulmonary edema, and the dependent portions of the body palpated for pitting indicative of subcutaneous edema. Edema is especially liable to develop after relatively small volumes of infusion in chronically ill individuals with low plasma protein content and in those with renal insufficiency Since continuous intravenous infusions have become widely used, an edematous condition of the viscera is revealed at necropsy by a considerable proportion of patients succumbing on surgical services. Jones, Eaton and White[16] have shown experimentally that in animals whose plasma proteins are lowered by suppuration, undernutrition or other cause, edema is readily produced by intravenous infusions; they speak of "experimental postoperative edema." Another possibility that must be borne in mind during large intravenous injections is that of cardiac failure. Altschule and Gilligan[1] found that when 500 to 1500 cc. of physiological saline or 5 per cent dextrose were injected into normal individuals at a rate of over 20 cc. per minute, the blood volume, venous pressure and velocity of blood flow rose, and increase in the work of the heart was revealed by a rise in cardiac output. Caughey and Richards[7] observed that when 1500 to 2500 cc. of normal saline were infused into normals at 50 cc. per minute, there was little change in venous pressure; in cardiacs, on the contrary, such an infusion produced a marked rise in venous pressure. Heart failure must therefore be watched for especially in individuals with previous cardiac disease But also in those with impaired renal function, notably when there is previous hypertension, one must be especially on guard against acute left ventricular failure with pulmonary edema. I have several times seen a normal arterial pressure rise to 150 or 160 mm. during the course of an intravenous drip in individuals with poor kidney function. However, apart from instances of previous heart disease, hypertension or renal insufficiency, it seems doubtful that cardiac failure is induced by even very large intravenous infusions given at a slow speed. When giving large intravenous infusions, the veins of the neck should be watched. Swelling of the cervical veins is an indication that the circulation is being overloaded and calls for slowing or discontinuance of the drip.

In forms of peripheral circulatory failure in which the electrolyte content of the body has been severely depleted (*e. g.,* protracted vomiting, diabetic coma following long-standing acidosis), hypertonic solutions of sodium chloride are often advantageously administered and may lead to much more rapid improvement than the isotonic solution Hypertonic salt solutions have been given in shock with the object of raising the blood volume and arterial pressure by osmotically drawing fluid from the tissues into the blood

stream. However, it is doubtful that much is accomplished along these lines for the salt leaves the blood stream rapidly and in many forms of shock the tissues are already dehydrated. When the latter circumstance obtains, it would appear undesirable to draw more fluid from the tissues. When hypertonic sodium chloride solution is administered, it should be for the object of replenishing the depleted electrolyte, and especially the sodium, content of the organism. If the injection of the hypertonic solution is carried out slowly, the amount of blood destruction is apparently insignificant One liter of 2 per cent sodium chloride solution or 300 to 500 cc. of 5 per cent solution may be given and followed by physiological salt solution Stronger sodium chloride solutions (10 or even 20 per cent) have been given, but I have no experience with them.

Ringer's Solution.—Because of its closer resemblance to the electrolyte pattern of the blood, Ringer's solution is extensively used in place of sodium chloride solution in the infusion treatment of shock. That the potassium and calcium contained in Ringer's solution are of specific value in shock remains to be demonstrated. Recent work (page 649) shows that the potassium of Ringer's solution is undesirable in the shock of Addison's disease.

Glucose Solutions.—Solutions of glucose afford a convenient and often valuable method of supplying water to the dehydrated organism and thus combating shock. In addition, dextrose solutions may be of value in the following ways:

(*a*) *In the circulatory collapse of diabetic acidosis and other forms* of ketogenic acidosis, the oxidation of the glucose tends to diminish the ketosis.

(*b*) When large quantities of glucose (200 to 300 grams in twenty-four hours) are given parenterally, the caloric value of the sugar may be significant in individuals who can take little by other routes.

(*c*) The oxidation of the glucose tends to spare body protein in individuals who take little by mouth and thus militates against the *azotemia that develops in shock.*

(*d*) In states of undernutrition in which the glycogen reserves of the liver have been depleted, the administration of glucose tends to replenish these stores and thus probably improves hepatic function and protects the liver from further damage.

(*e*) Glucose infusions are often followed by increase in urinary volume. This is presumably due to greater renal blood flow resulting from increase in circulating blood volume.

Because of these important advantages, solutions of glucose are now very generally administered in shock. The fact is sometimes lost sight of that when depletion of electrolyte is concerned in the pathogenesis of shock (*e. g.*, in vomiting and in diabetic acidosis) the injection of glucose and water alone does not restore the framework of electrolytes on which the circulating blood volume is main-

tained (page 643). For this reason, whenever loss of electrolyte participates in the causation of shock, sugar solutions alone do not suffice and salt must be administered. Of course, it may be advantageous to give both glucose and sodium chloride.

Five per cent glucose solution is approximately isotonic with blood and this is the strength most often used for intravenous or subcutaneous administration However, if it is desired to inject a large amount of sugar to combat undernutrition, ketosis, or liver damage, a 10 per cent solution may be used In recent years, 25 per cent and 50 per cent glucose solutions have been extensively injected in shock. The object has sometimes been to draw tissue fluid into the blood stream and thus increase the circulating blood volume, elevate arterial pressure, and augment urinary volume. However, the tissues are most often dehydrated in shock and further exsiccation would seem undesirable. In individuals with heart disease, care must be exercised in the injection of hypertonic solutions because of the danger of cardiac strain, which I have several times seen in elderly patients with coronary sclerosis; the basis for the cardiac strain is indicated by Ellis and Faulkner's[12] finding that the intravenous injection of 100 cc. of 50 per cent glucose was followed by an average rise of 13 per cent in blood volume within a minute of the completion of the injection The writer can see little use in shock for the injection of 50 per cent glucose solution apart from hypoglycemia and perhaps in some instances of increased intracranial tension. Even in increased intracranial tension, the desirability of concentrated glucose solutions is not always evident, for Masserman[22] has found that the fall in cerebrospinal fluid pressure is followed by a rise above the previous level due to the entrance of the glucose into the cerebrospinal fluid. The latter objection is overcome by the use of sucrose.

Fifty per cent solution of *sucrose* in amounts of 100 to 200 cc intravenously has also been used in the treatment of shock. Such injections do increase the blood volume. However, this effect is transitory and attained only by further dehydration of the tissues. The injection of sucrose would thus appear to have little basis in the treatment of shock, and in actual practice I have not observed benefit.

Alkaline Solutions.—Protracted acidosis, through the intermediacy of loss of fixed base and dehydration, can lead to peripheral circulatory failure and shock; the outstanding example is the circulatory collapse of diabetic acidosis. In other forms of shock, such as traumatic shock, the circulatory disturbance may produce acidosis (page 624), which then presumably aggravates the circulatory failure and thus produces a vicious cycle. In the light of these facts, it is not surprising that the administration of alkalis has repeatedly been recommended as a therapeutic measure when shock is accom-

arterial pressure and other manifestations of peripheral circulatory failure. Theoretically, one would anticipate more benefit from vasoconstrictor drugs in the forms of shock—primary traumatic shock, some forms of circulatory collapse in the infectious diseases, spinal anesthesia and some types of fainting—which are due to relaxation of the small vessels. Actually, one does sometimes see good, if transient, effects in such cases.

The drugs most often administered in shock with the intention of producing vasoconstriction are the following:

Epinephrin is the most powerful vasoconstrictor in general use. It may be injected subcutaneously or intramuscularly in doses of 0.5 to 1 mg; when the circulation is severely depressed, it should be given intravenously in a somewhat smaller dose. Epinephrin is often added to an intravenous drip of salt or dextrose solution; the dilution is so high that the efficiency of this method of administration seems doubtful. I have several times seen favorable results from several injections daily of epinephrin in pneumonia and other infections. It has already been mentioned that epinephrin is of help in rare instances of severe shock due to coronary thrombosis; here it probably acts mostly as a cardiac stimulant. I have often given epinephrin in the various forms of shock due to dehydration; while there was often a transient rise in arterial pressure, the ultimate course was hardly influenced, except perhaps for some instances of diabetic coma. *Ephedrin* may be used in place of epinephrin in the hope of producing longer lasting though less powerful vasoconstriction. Recently, Altschule[3] and his associates have recommended *paredrine* for the same purpose. They found that paredrine has a rather prolonged pressor action with rise in both the systolic and diastolic arterial pressures and also elevation in venous pressure; this was due to stimulation of the muscle of the small vessels. The drug had little effect on the heart. Altschule and Gilman[4] found paredrine very effective in combating fall in blood pressure due to spinal anesthesia. They used doses of 20 to 30 mg orally, 10 to 20 mg. intramuscularly, or 5 to 10 mg. intravenously. Further observations would seem desirable to learn whether paredrine is preferable to the previously mentioned sympathicomimetic amines in the treatment of shock.

The posterior lobe of the *pituitary* gland contains a vasoconstrictor principle which may elevate the arterial pressure in shock. It may be injected intramuscularly either in the form of the official solution of posterior pituitary (0.5 to 1 cc.) or the equivalent amount of pitressin, repeated in an hour. In my experience, pituitary extract has been much less efficient than epinephrin in elevating arterial pressure in shock.

Caffein is given to a large proportion of patients in shock, including most of those who seem to be dying. The conception is that

caffein stimulates the medullary vasomotor and respiratory centers and increases the accomplishment of the heart. The injection of caffein is sometimes followed by a small rise in arterial pressure and perhaps improvement in the depressed sensorium, but the effects are rarely more than transitory. It should be borne in mind that caffein may aggravate restlessness and interfere with sleep. Caffein is usually injected intramuscularly; about 0.5 gram of caffein sodium benzoate may be given and repeated at intervals of two or three hours if necessary. If the depression of the circulation is extreme, caffein may be administered by slow intravenous injection

Camphor is often administered to patients in shock as a cardiac and vasomotor stimulant About 2 cc. of the 10 per cent solution in olive oil may be administered intramuscularly. Painful indurations often result. I have not seen benefit from the injection of camphor, or any significant effect from its more recently introduced derivative cardiazol

Recently, Warfield[29] and others have advocated *strychnin* in the treatment of peripheral circulatory failure, especially in the acute infections Warfield recommends relatively high doses, from $\frac{1}{20}$ to $\frac{1}{15}$ grain subcutaneously every two or three hours. He feels that with such dosage strychnin may be life-saving in the circulatory collapse of influenzal pneumonia and other infections. Since strychnin increases the tone of the skeletal muscles, such success as is attained with it is theoretically interesting in the light of Henderson's theory of the rôle of diminished muscle tone in the pathogenesis of shock (page 629). In my small experience, strychnin has produced no striking effect, but it may be that the dosage was too small

The drugs just enumerated include most of those which are administered to a large proportion of patients dying from any cause, most often as much for the treatment of the relatives as of the patient Of all, the only one from which the writer has seen pronounced effects in peripheral circulatory failure is epinephrin, and that but rarely in forms of peripheral circulatory failure due to anhydremia.

ADRENAL CORTICAL HORMONES

For many years, under the influence of the hypothesis that many forms of shock are due to functional inadequacy of the adrenal cortex, attempts have been made to treat shock with adrenal cortical preparations In view of the slight activity of such preparations until the past few years, it is not surprising that they met with little or no success. But since the introduction of more active preparations, the attempt to treat shock by adrenal cortical preparations has had better results. Particularly promising is the use of the synthetic *adrenal cortical hormone, desoxycorticosterone acetate.*

In the oligemic forms of shock due to loss of sodium chloride and

water, the use of adrenal cortical extracts seems well founded, for they favor the retention of salt and water in the body, even to the extent of producing edema. With desoxycorticosterone acetate, I have been able to make a patient with malignant disease gain 20 pounds in weight with the development of edema and transudates into the pleura and peritoneum. Perla[24] and his associates have shown that in rats and mice treatment of histamine shock with both desoxycorticosterone acetate and sodium chloride solution is more effective than the administration of salt and water alone. Finally, in the treatment of Addison's disease with desoxycorticosterone acetate, the blood pressure rises not only to normal but often disagreeably far above normal; and it seems that this effect on the blood pressure does not closely parallel the effect on the blood volume and may be due to independent effect on the tone of the small vessels.

There would thus seem to be ample reason for believing *a priori* that adrenal cortical hormones may be of value in the treatment of shock. Some recent experiences are in accord with this conception Perla[24] and his associates found that the preoperative administration of desoxycorticosterone acetate together with considerable quantities of salt and water tends to prevent surgical shock. Ragan[25] *et al.* found that desoxycorticosterone acetate averts the fall in plasma volume which follows anesthesia and operation. Fine[13] and his coworkers observed that desoxycorticosterone acetate prevents the decrease in plasma volume that results from intestinal obstruction In one patient observed by the writer, who was suffering from nausea, vomiting and a shock-like state due to roentgen-ray treatment for malignant disease, the administration of desoxycorticosterone acetate produced not only water and salt retention but was also followed by disappearance of the nausea and vomiting and great improvement in the general condition. Unfortunately, desoxycorticosterone acetate as usually given by intramuscular injection (5 to 20 mg. doses) is absorbed rather slowly. For intravenous administration with quick action, cortin or other aqueous preparations are needed, and expensively large quantities are necessary to obtain equal effects. Further investigation is required to establish to what extent the administration of adrenal cortical hormones improves the results obtained in the treatment of shock with large quantities of salt or transfusion A few observations in this regard by Dr. Frank Engel and the writer were not conclusive.

OTHER MEASURES IN THE TREATMENT OF SHOCK

Elevation of the foot of the bed tends to aid venous return from the lower extremities to the heart and perhaps militates against cerebral ischemia Warfield[26] found that in the circulatory failure of typhoid fever, this simple measure may slow the rate and increase

the volume of the pulse. He also found that bandaging the lower extremities is of value in shock; the original use of the procedure was empirical but a rationale has been afforded by Wollheim's[10] observation that it increases the circulating blood volume as much as 1 liter. The increase in circulating blood volume is presumably due to the squeezing out of the capacious blood depots in the skin (page 64) and other parts of the lower extremities

It is customary to attempt to keep patients in shock warm by wrapping them in blankets and applying hot-water bottles and other heating devices. This is undoubtedly a valuable procedure for loss of body heat appears to favor shock and cold may predispose to the development of pneumonia But it should be remembered that in peripheral circulatory failure cold extremities often accompany an elevated internal temperature, as revealed by a rectal temperature of 103° F. or even more In such cases, the coldness of the extremities is at least partly due to the vasoconstriction that (page 631) serves a useful purpose by diverting a larger portion of the small cardiac output to the more immediately vital portions of the body. For this reason, it is at least theoretically possible that excessive application of heat to the surface of the body, through increasing the oxygen consumption of the superficial tissues and necessitating increased blood flow through them, may tend to neutralize an important defensive mechanism.

Morphine may be necessary to control restlessness or pain. However, excessive dosage with its attendant depression of the medullary centers is to be carefully avoided in shock, a condition in which the final collapse is probably engendered by deficient blood flow through these centers.

Oxygen is nowadays given to a large proportion of patients succumbing to shock, especially on surgical services. In the presence of pneumonia or other pulmonary lesions which produce arterial anoxemia, oxygen is of course indicated. In the absence of pulmonary lesions, the indication for oxygen is not so clear-cut. Apart from cases with lung changes, the cyanosis of shock is of peripheral origin —due to diminished volume of blood flow with consequent increased reduction of hemoglobin in the capillaries—which might lead one to think that the tissue anoxia would not be affected by inhalation of high concentrations of oxygen. However, it is likely that the inhalation of 100 per cent oxygen may raise the arterial oxygen pressure to such high levels as to compensate to some extent for the diminished blood flow and thus tend to relieve tissue anoxia (*cf.* page 740).

Finally, it may be mentioned that not only is *digitalis* not indicated in peripheral circulatory failure, but would appear to be contraindicated because of its tendency to decrease the circulating blood volume (page 709).

APPLICATION OF THE FOREGOING MEASURES IN INDIVIDUAL FORMS OF SHOCK

Hemorrhagic Shock.—Transfusion is the obvious remedy for shock due to hemorrhage. *It should be borne in mind that immediately after a large hemorrhage, before considerable amounts of tissue fluid have reëntered the blood stream, the hemoglobin percentage is unaltered.* Nevertheless, the symptoms of shock are due to the loss of blood with its entailed decrease in circulating blood volume, and transfusion is indicated with an urgency proportional to the severity of the drop in arterial pressure and other manifestations of peripheral circulatory failure. When hemorrhage occurs in previously dehydrated patients, as is often the case in peptic ulcer with vomiting, transfusion should be supplemented by the intravenous administration of sodium chloride solution. The latter alone is often of great help when transfusion is not feasible in an emergency.

Traumatic Shock.—In the treatment of secondary shock, the task is twofold. *to prevent further repercussions from the traumatized area on the organism, and to improve the failing circulation.*

The measures called for in the traumatized area will not be discussed here Suffice it to say that it is of the utmost importance to ascertain the presence of occult bleeding and to take measures to stop it; *in the presence of shock, even small losses of blood are ominous and account for many deaths.* The patient should be protected from cold and, before he is moved, further damage to the tissues with resultant bleeding prevented as far as possible by splinting. Pain and restlessness call for morphine, but in the presence of a failing circulation large doses of the narcotic are harmful; I have several times seen this evidenced by the addition of cyanosis to the previous pallor. The question of whether the patient can tolerate any considerable operative procedure before measures are taken to improve the circulation often calls for nice surgical judgment. However, continued loss of blood may necessitate intervention despite a critical state. Because of the low arterial pressure, gas oxygen is usually the preferable anesthetic and spinal anesthesia is contraindicated.

Efforts to improve the circulation are carried out along the lines already described. These consist in the administration of fluids with the object of elevating the circulating blood volume. The fact that the peripheral vessels are already constricted accounts for the usual lack of benefit from epinephrin and other vasoconstricting drugs. Where blood has been lost, transfusion is called for, and this is often beneficial even in the absence of gross bleeding. While it is true that a large portion of sodium chloride and glucose solutions leaves the blood stream quickly, nevertheless enough may be

retained for a sufficient time to elevate the arterial tension and ameliorate other manifestations of circulatory failure. When the shock is of considerable duration, acidosis often develops, and under these circumstances intravenous injection of an alkaline solution may be followed by rise in arterial pressure and improvement (Coonse *et al.*[10]). The value of the adrenal cortical preparations mentioned above remains to be determined.

In primary traumatic shock, and in shock due to spinal anesthesia or the perforation of a hollow viscus, the injection of epinephrin is called for and sometimes produces a prompt rise in arterial pressure. It may be followed by ephedrin.

Surgical Shock.—Appreciation of the fundamental pathogenetic rôle of factors tending to decrease the circulating blood volume has contributed notably in recent years to lessen the incidence of surgical shock Preliminary to the operation the patient should be supplied with ample fluids, parenterally if necessary If vomiting or other cause has led to dehydration, this should be remedied as far as possible. Vigorous catharsis with its attendant dehydration is to be avoided. While preservation of body heat is, of course important, excessive sweating for long periods while wrapped in hot blankets is not desirable. It goes without saying that every effort is to be made to minimize the loss of blood and avoid unnecessary handling of tissues, for this results in the seeping of remarkably large volumes of fluid rich in plasma protein, the conservation of which is so desirable During protracted operations, and especially if the patient is dehydrated, it may be wise to administer glucose or salt solution by intravenous drip, if necessary, citrated blood may be given by the same method. Following the operation, adequate fluids are to be administered. Especially Coller[9] and his associates have pointed out how large are the quantities of fluid lost during and after major operations They estimate that the sick surgical patient needs a daily ration of 3500 cc. of water (2000 cc. to replace vaporization and 1500 cc. for the formation of urine) plus the amount lost by vomiting or discharge and an additional increment if dehydration was present before operation. If there is vomiting, diarrhea, or large amounts of discharge, it is important that the lost electrolyte be replaced by the administration of sodium chloride. The detailed studies of Chabanier and Lobo-Onell[8] indicate that postoperative shock is almost always accompanied by hypochloremia (and doubtless, what is more important, by deficiency of base) Robineau and Lévy[26] have found that the intravenous injection of hypertonic sodium chloride solution (300 to 500 cc. of a 4 per cent solution daily) for several days after operation serves to lessen the incidence of postoperative shock and to improve intestinal motility with decrease in distention. I have also seen excellent results from hypertonic salt solution in postoperative shock, especially where

vomiting was concerned. However, where there is no reason to assume great loss of electrolyte, the administration of excessive quantities of salt solution is to be avoided. Especially where nutrition has suffered with consequent depression of the plasma proteins, edema may result from large saline infusions (Jones, Eaton and White[16]) and with the general popularity of the infusion treatment of shock is becoming increasingly common on surgical services. Coller[9] and his associates have shown that glucose solution leads to less water retention than does salt solution. But where there is actual dehydration, especially when manifestations of peripheral circulatory failure are present, sodium chloride is an important element in the treatment. If inability to ingest sufficient food threatens exhaustion of the glycogen reserve with consequent ketosis and perhaps liver damage, sugar is to be included in the infusion. When hemorrhage is concerned in the causation of surgical shock, or anemia is present, transfusion is called for. The possible prophylactic and therapeutic value of adrenal cortical preparations in surgical shock is discussed above (page 804).

Diabetic Acidosis.—Through mechanisms already discussed (page 646), diabetic acidosis may lead to peripheral circulatory failure Indeed, the sugar and bicarbonate content of the blood may be restored to normal, and nevertheless the patient succumb with the clinical picture of shock. We have seen that the circulatory collapse is apparently a result of loss of water and electrolytes For this reason, even though there is no evidence of circulatory failure, it is important that large amounts of water and sodium chloride be supplied as a measure for the prophylaxis of shock. If the patient cannot take the water and salt by mouth, it should be administered subcutaneously or intravenously.

When evidences of peripheral circulatory failure have appeared, the necessity for large amounts of water and sodium chloride is all the more urgent. There can be no doubt that in the past many patients with diabetic coma have succumbed because attention was concentrated too completely on the correction of the disturbance in carbohydrate metabolism by the administration of insulin, while too little fluid and salt were supplied to overcome the deficiency of these substances. The development of such manifestations as fall in arterial pressure, cold extremities, cyanosis, obvious dehydration of the skin, and softness of the eyeballs call for large quantities of water and sodium chloride. In addition, there is good reason to believe (page 623) that the azotemia which so often accompanies diabetic coma, or may even first appear after coma has been relieved by insulin (McCance and Lawrence[21]) is a manifestation of deficient blood flow through the kidney due to circulatory failure produced by dehydration and salt deficiency. In accord with this conception, Blum[6] showed that many instances of oliguria with resultant azo-

temia in diabetic coma can be relieved only by the administration of large amounts of sodium chloride.

When any of these evidences of peripheral circulatory failure appear in diabetic acidosis, it is probably wise to administer sodium chloride solution intravenously; many of the patients cannot take sufficient fluids by mouth or rectum and the circulation may be too greatly depressed to permit of sufficiently rapid absorption from the subcutaneous tissues. Often, excellent results are obtained by the administration of physiological salt solution. It is frequently advantageous to administer 3 or 4 liters of such solution in twenty-four hours. Five per cent or even more of glucose may be added to the salt solution, as dictated by the blood sugar and the dosage of insulin; the questions of the administration of insulin and glucose in diabetic coma will not be discussed. But it is to be emphasized that when peripheral circulatory failure due to dehydration and loss of salt is present in diabetic acidosis, this cannot be remedied by the administration of glucose alone; the lost electrolyte must be replaced In some cases with severe depletion of the sodium and chloride contents of the blood in which shock is immediately threatening, improvement is hastened by the administration of hypertonic sodium chloride solution, which is life-saving in some cases that do not respond to physiological salt solution (Root[27]). Three or four hundred cubic centimeters of 5 per cent sodium chloride solution by intravenous drip may produce quick improvement in the circulation and decrease in azotemia. In cases in which the acidosis is severe, as evidenced by a carbon dioxide combining power of less than 25 volumes per cent, alkaline solutions (sodium bicarbonate or sodium lactate, see above) should be substituted for the sodium chloride solution. When the carbon dioxide combining power is less than 15 volumes per cent the necessity for alkali is very pressing. Largely as a result of Joslin's[17] observations, the administration of alkali in diabetic coma was thought to have been rendered unnecessary by the introduction of insulin. However, most recent investigators (Hartmann[14] and Baker[4]) have found that alkali is of value in severe diabetic acidosis, and this has also been the experience of the writer The severe acidosis is undoubtedly a factor in the production of many instances of peripheral circulatory failure, and its elimination enhances the chances of recovery from diabetic coma.

Lawrence[18] and Labbé and Boulin[18] have found that the intravenous injection of epinephrin is of value in the peripheral circulatory failure of diabetic coma and I have made similar observations.

Addison's Disease.—The peripheral circulatory failure characterizing the crises of Addison's disease is treated with large volumes of sodium chloride solution and cortical extract or desoxycorticosterone acetate. In desperate situations hypertonic sodium chloride

solution and cortical extract should be injected intravenously. Glucose should also be given to combat hypoglycemia. By these measures patients who in the past would undoubtedly have succumbed may be restored to excellent condition and sometimes so maintained for a considerable time But sooner or later the treatment fails; it would appear that commercial preparations vary widely in potency —some are entirely without value—and they do not always contain all the principles of the suprarenal gland necessary to survival. It may be, but is not yet proven, that the use of desoxycorticosterone acetate will remedy this deficiency. In the effort to prevent acute crises of suprarenal insufficiency, the patient should have a diet containing a large amount of sodium chloride and, if necessary and economically feasible, cortical extract. Implantation of pellets of desoxycorticosterone acetate by the ingenious method of Thorn[34] and his associates may prove to be an excellent method of treatment, but one must keep watch for the development of hypertension The recent work mentioned on page 649 indicates that the intake of potassium should be restricted as far as possible.

Vomiting and Diarrhea.—Peripheral circulatory failure due to these disturbances is effected through the intermediacy of loss of electrolyte. The rational treatment thus includes administration of large amounts of sodium chloride solution, usually best injected intravenously In urgent circumstances, it is usually wise rapidly to replace some of the lost electrolyte by intravenous injection of hypertonic sodium chloride solution (300 to 400 cc. of the 5 per cent solution) followed by a continuous intravenous drip of large volumes of 5 per cent glucose in physiological salt solution. It should be remembered that glucose and water alone will not replace the electrolyte lost by vomiting or diarrhea. In paralytic ileus, the enhancement of intestinal motility by hypertonic salt solution may also be of value.

The Acute Infections.—It has been seen in previous chapters that, apart from rheumatic fever and diphtheria, circulatory collapse in the febrile infections is almost always due to peripheral circulatory disturbance and not to cardiac failure. The peripheral circulatory failure produces the clinical picture of shock and its treatment is that outlined above. The intravenous injection of large volumes of sodium chloride and glucose solution is often of great value. If the arterial pressure has fallen, injection of epinephrin may be of aid, as indicated by rise in pressure and amelioration of other symptoms of circulatory failure. Though so often given, digitalis is not indicated in the peripheral circulatory failure of the infections. This is to be emphasized especially in the case of pneumonia. In pneumonia, quite as well as in the other acute infections, circulatory failure in those who enter the disease with a healthy heart is almost always of peripheral origin (page 667). For this reason, routine

digitalization of patients with pneumonia is to be condemned The carefully controlled investigation of Wyckoff, Du Bois and Woodruff[31] furnished strong evidence on this point. They gave digitalis to alternate patients with pneumonia, and found that the mortality was greater in those who received the glucoside. It would thus appear that digitalis should be administered only to those patients with pneumonia who have antecedent heart disease or who show definite evidences of heart failure in the form of engorgement of the lesser or greater circulations. That pulmonary edema in pneumonia is not due to heart failure and thus does not call for digitalis has already been pointed out (page 666)

Burns.—When shock develops in the first days after widespread superficial burns, the evidence is strong that the peripheral circulatory failure is due to decrease in plasma volume consequent on inflammatory exudation in the burned area In the subsequent course of burns, the factors of secondary infection and the absorption of toxic substances may be concerned in the production of the clinical picture. But in the first days the constitutional manifestations are those provoked by the decrease in plasma volume. The therapy indicated by this pathogenesis is the administration of large volumes of fluid. Inasmuch as the chloride content of the blood is low, it would appear that sodium chloride solution with or without dextrose rather than dextrose solution alone should be given. Penick[23] suggests that as much as 100 cc per kg body weight should be given each twenty-four hours, usually, the intravenous drip is used. The administration of large volumes of salt solution often has excellent effects. Since the red cell count is usually much elevated by the decrease in plasma volume, transfusion, though often used, does not appear indicated.

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